Endocrine System

(HORMONES)

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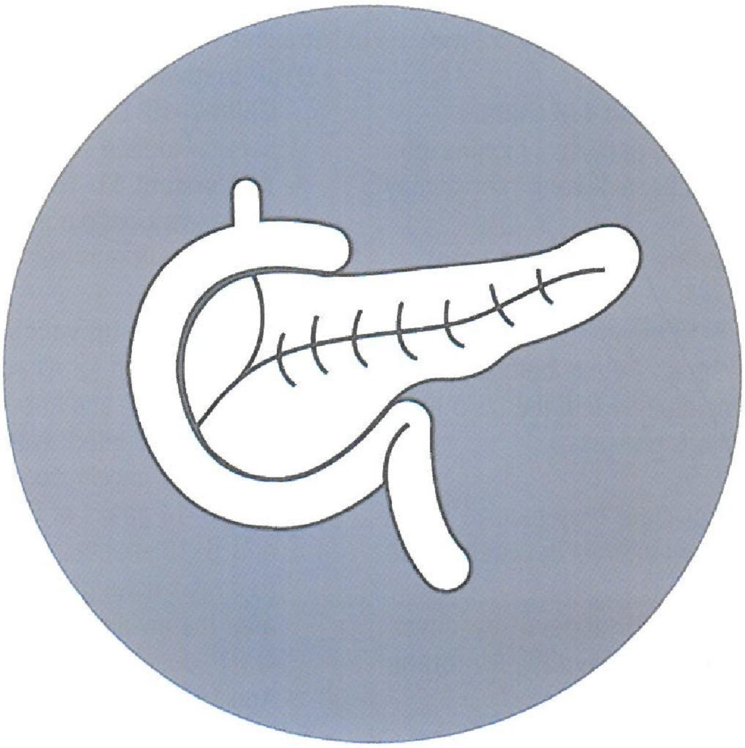
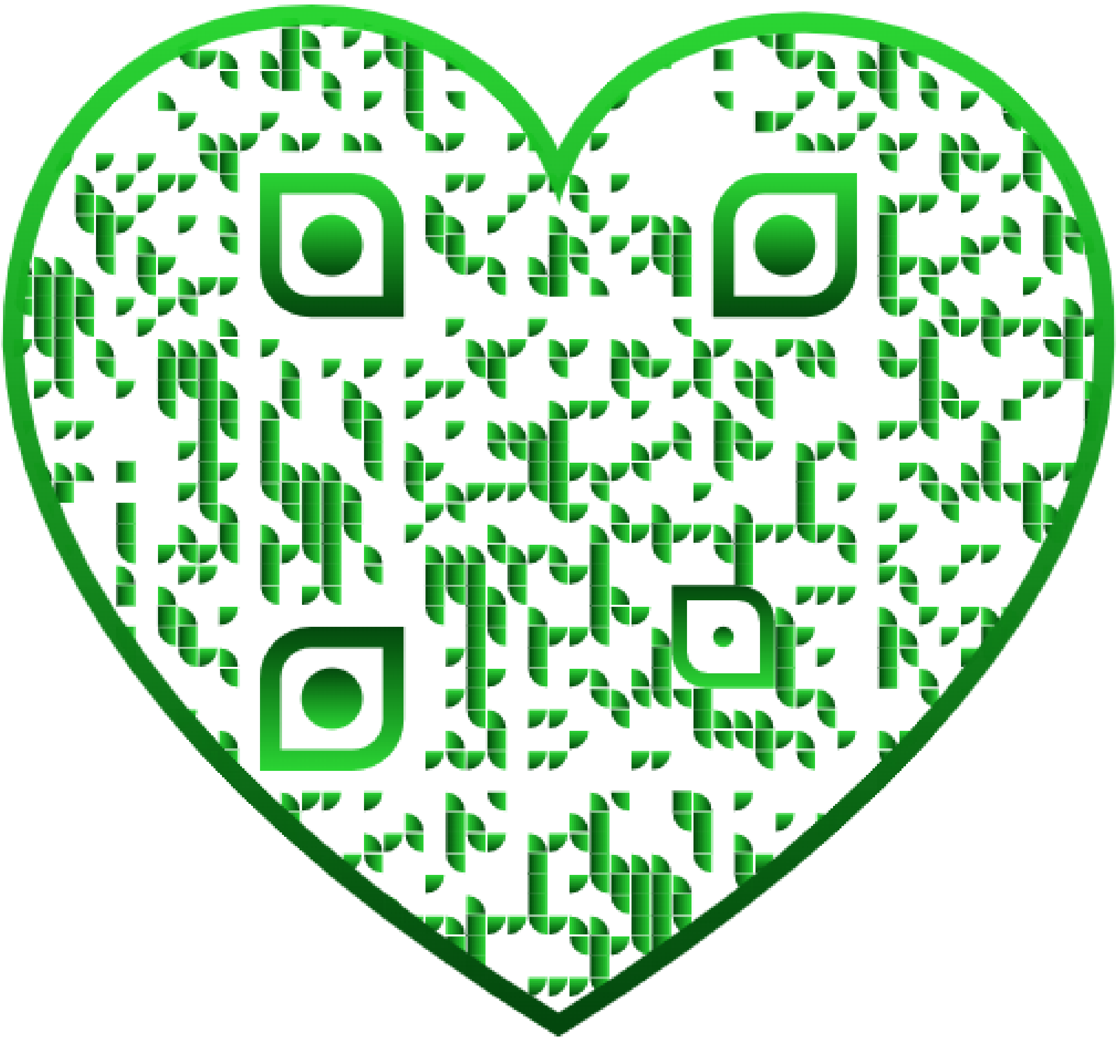
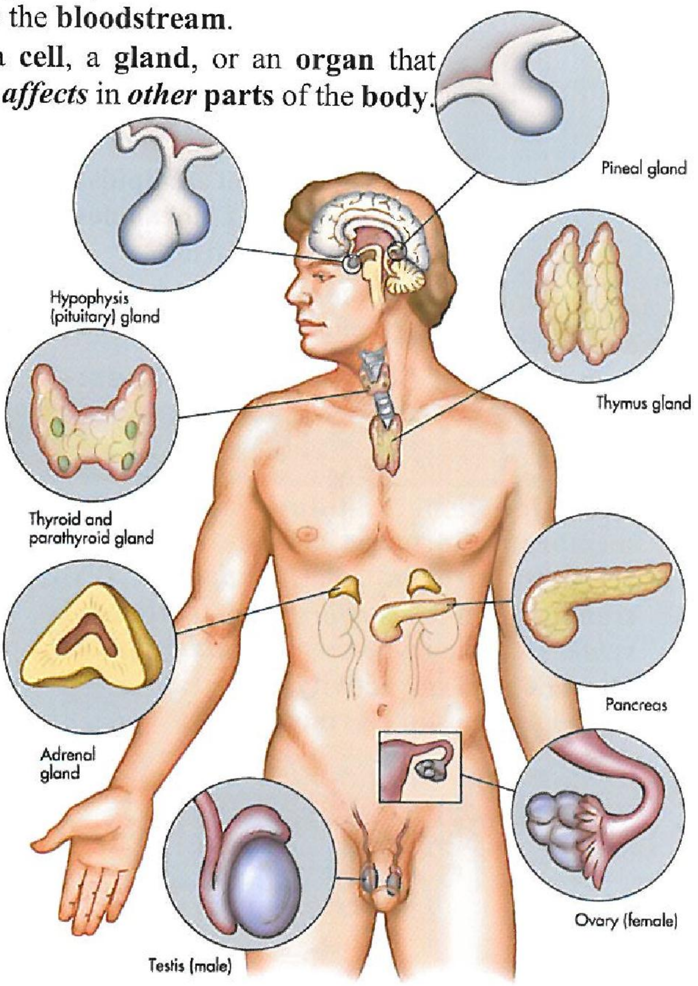




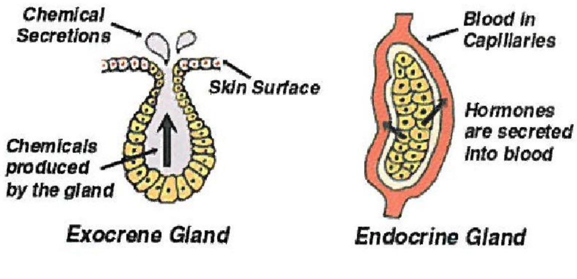
Introduction

➢ Overview:-

- **Endocrine System**; is the ***system*** of **glands**, each of which **secretes** ***different types*** of **hormones *directly*** *into* the **bloodstream**.
- **Hormone**; is a **chemical *released by*** a **cell**, a **gland**, or an **organ** that ***transported by*** the **circulatory system** & ***affects*** in ***other*** **parts** of the **body**.


Pineal gland
Hypophysis (pituitary) gland
Thymus gland
Thyroid and parathyroid gland
Pancreas
Adrenal gland
Ovary (female)
Testis (male)

- **Hormones** *have* **major role** *in*:
  - ***Regulation*** of **metabolism**.
  - ***Control*** of **growth**.
  - ***Regulation*** of **sex functions** and **reproduction**.
  - **Homeostasis** (ability to maintain a constant internal environment in response to environmental changes).
  - ***Resistance*** of **stress**.
- **Major endocrine glands** *include*;
  - **Pineal gland**
  - **Pituitary gland**
  - **Thyroid gland**
  - **Parathyroid gland**
  - **Thymus gland**
  - **Adrenal glands**
  - **Pancreas**
  - **Ovaries**
  - **Testes**
- **Types of glands**;
  - A) **Exocrine Glands**;
    - ***Release*** their **cellular secretions** through a **duct** which ***empties*** to the **outside** or ***into*** the **lumen** of an **organ**.
    - *Such as*; **sweat glands**, **salivary** and **pancreatic glands** and **mammary glands**.
    - ***Not*** **considered** a **part** of the **endocrine system**.
  - B) **Endocrine Glands**;
    - ***Not*** **contain duct** and ***release*** their **secretions *directly*** into the **bloodstream**.
    - ***Collection*** of **endocrine glands** *makes up* the **endocrine system**.


Chemical Secretions
Skin Surface
Chemicals produced by the gland
Blood in Capillaries
Hormones are secreted into blood

Exocrene Gland **Endocrine Gland**

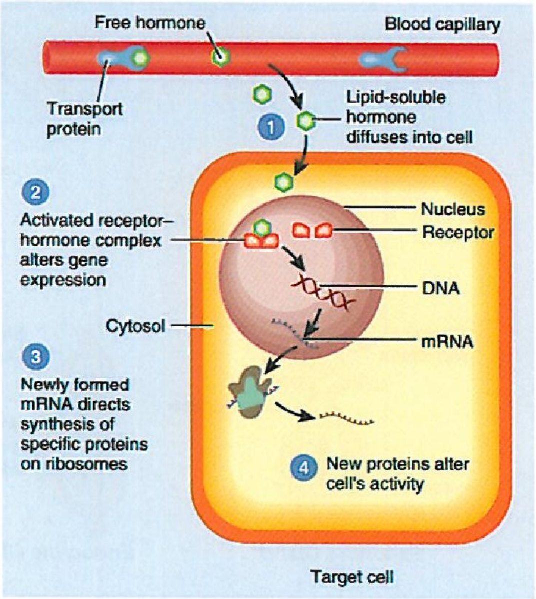
- *N.B.*;
  - **Kidney**, **liver**, **heart** and **gonads** have ***secondary*** **endocrine functions**;
    - *For example*; - **Kidney *secretes*** **endocrine hormones** such as **Erythropoietin** and **Renin**
    - - **Heart *secrete*** **Atrial Natriuretic Peptide** (**ANP**).
    - **Gonads** are the **organs** that ***make*** **gametes**; **testes** in **males** and **ovaries** in **females**.
  - **Axis**; a ***number*** of **glands** that **signal *each other*** in **sequence**, *such as* **hypothalamic-pituitary-adrenal axis**.
  - **Paracrine Signaling** or **Paracrine Factors**; is a **cell-*to*-cell communication** in which a **cell *produces*** a **signal** to ***induce changes*** in **nearby cells**, ***altering*** the **behavior** of ***those*** **cells**.
  - **Autocrine** or **Intracrine Signalling**; A **hormone** that ***acts inside*** a **cell**, ***regulating*** **intracellular events**, *such as* **steroid hormones** *act through* **intracellular** (nuclear) **receptors**.

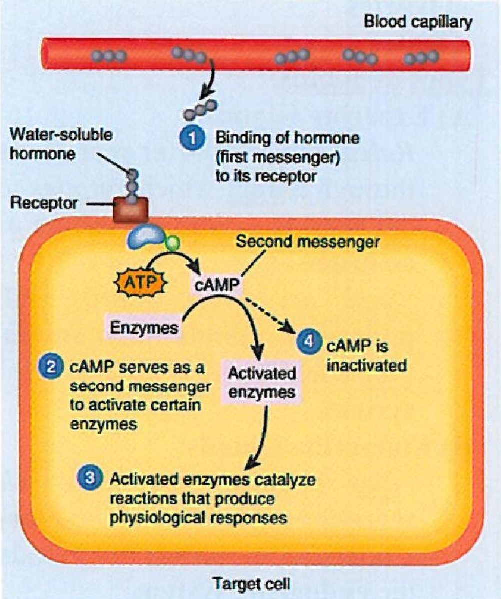
➢ Chemical Classification of Hormones:-

Amino acid-derived	- **Hormones** that ***derived from*** the **amino acids**. - *Examples*; **Melatonin** and **Thyroxine**.
Polypeptide and Proteins	- **Hormones** that are ***chains*** of **amino acids**. - *Examples*; **Insulin** and **Growth Hormone**. - ***Some* protein hormones** are actually **glycoproteins**, ***containing* glucose** or other **carbohydrate *side-chains***. - *Examples*; **Luteinizing Hormone** (**LH**), **Follicle-stimulating Hormone** (**FSH**) and **Thyroid-stimulating Hormone** (**TSH**).
Steroids	- **Hormones** that are **lipids**, ***synthesized from*** **cholesterol (steroidal structure)**. - *Examples*; **sex hormones Estradiol** and **Testosterone** as well as the **stress hormone Cortisol**.
Eicosanoids	- **Hormones** that ***derived from*** **lipids**. - *Examples*; **Leukotrienes** and **Prostaglandins** (see Autacoids Chapter).

➢ Mechanism of Action of Hormones:-

Lipid-soluble Hormones (Intracellular Receptors)	**Water-soluble Hormones** (Cell Membrane Receptors)
- **Genomic action**; *by* **diffuse** *through* the **cell membranes** of **target cells** then ***binds to*** a **receptor protein** that ***activates*** **DNA transcription** of ***specific*** **genes** → ***m*RNA** → ***synthesis*** of **enzymes** → ***regulate*** **specific physiological cell activity**. - *Examples*; **Steroid Hormones**.	- **Non-Genomic action**; *by* **binds** to a **receptor protein** on the **cell membrane** of the **cell** → ***stimulates*** **production** of ***second*** **messengers**. - **Second messengers** *such as* **cAMP**, **IP3**, **Calcium-calmodulin *system*** and **cGMP**. - *Examples*; **Protein**, **Polypeptide** and *most of* **Amino Acid Hormones**.


Free hormone
Blood capillary
Transport protein
1
Lipid-soluble hormone diffuses into cell
2
Activated receptor–hormone complex alters gene expression
Nucleus
Receptor
DNA
Cytosol
mRNA
3
Newly formed mRNA directs synthesis of specific proteins on ribosomes
4
New proteins alter cell's activity
Target cell


Blood capillary
1
Binding of hormone (first messenger) to its receptor
Water-soluble hormone
Receptor
Second messenger
ATP
cAMP
Enzymes
2
cAMP serves as a second messenger to activate certain enzymes
Activated enzymes
4
cAMP is inactivated
3
Activated enzymes catalyze reactions that produce physiological responses
Target cell

➢ Regulation of Hormone Release:-

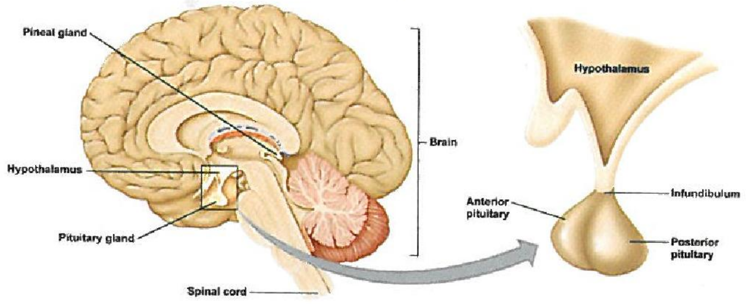
A) Control of Hormone Secretion

Negative **feedback (-)**	***Positive*** **feedback (+)**
- ***Increase*** in **hormone *inhibits*** *further* **secretion**. - *Example*; - ↑ T_3 & T_4 → ↓ TSH → ↓ T_3 & T_4. - ↓ T_3 & T_4 → ↑ TSH → ↑ T_3 & T_4.	- ***Increase*** in **hormone *stimulate*** *further* **secretion**. - *Example*; Uterine contractions → ↑ Oxytocin → ↑↑ contractions→ ↑↑ Oxytocin

B) Receptor Regulation

***Down*-regulation**	***Up*-regulation**
- **Prolonged *increase*** in **hormone secretion *decrease number*** of **cell receptors** and *thereby* ***decrease*** **cell response**.	- **Prolonged *decrease*** in **hormone secretion *increase number*** of **cell receptors** and *thereby* ***increase*** **cell response**.

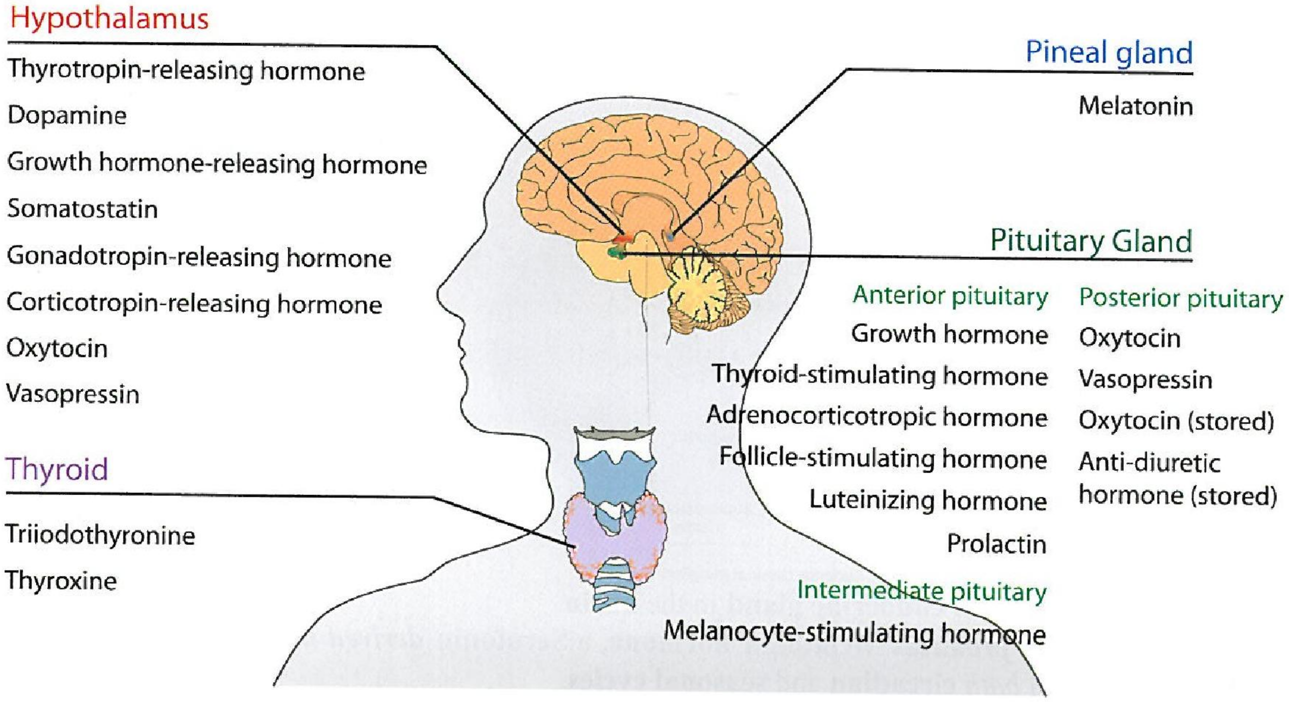
Hypothalamus

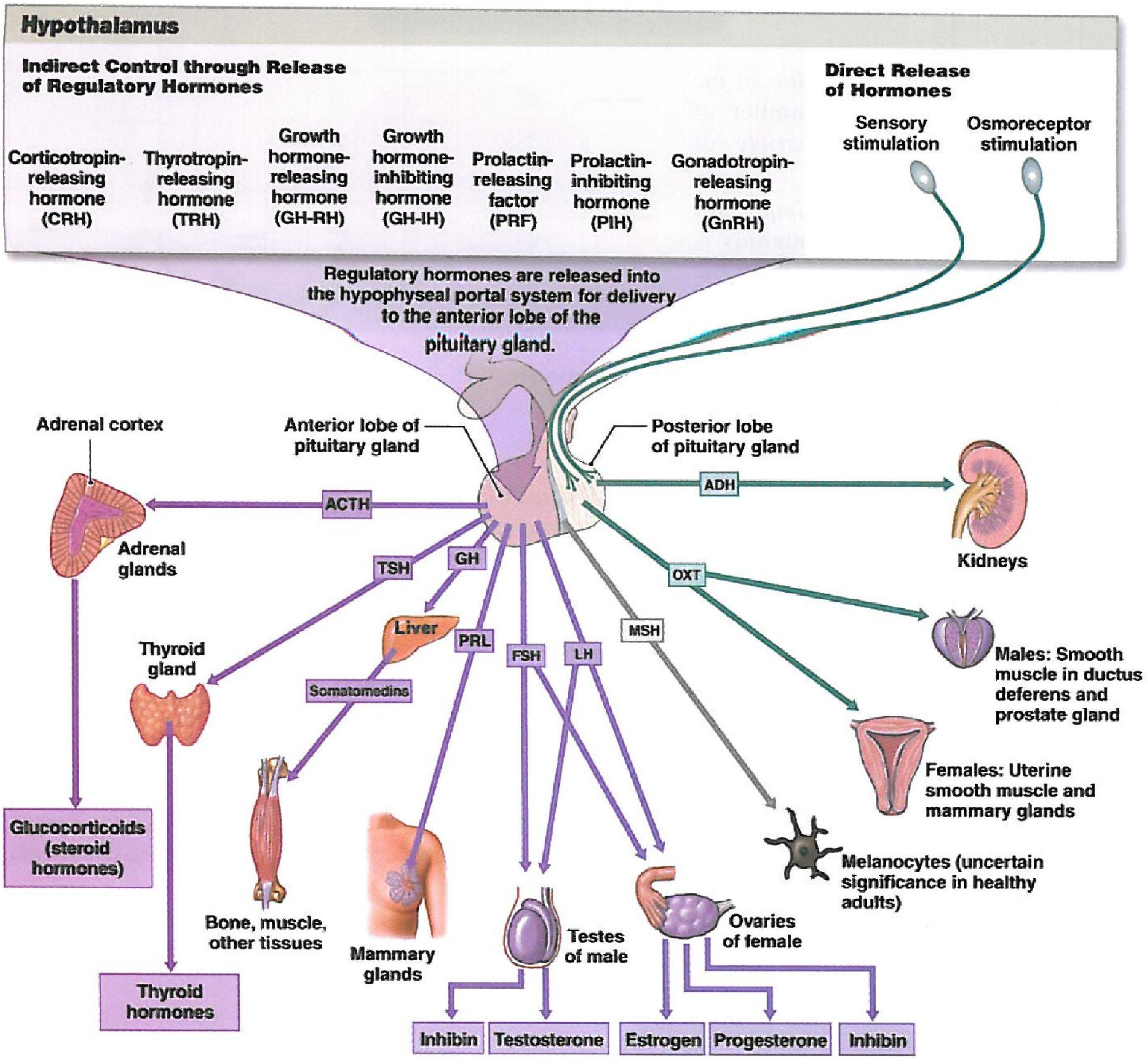

Pineal gland
Hypothalamus
Pituitary gland
Spinal cord
Brain
Hypothalamus
Anterior pituitary
Infundibulum
Posterior pituitary

- **Hypothalamus** is a *portion* of the **brain** that *contains* a **number** of *small* **nuclei** *with* a *variety* of **functions**.
- **One** of the *most important* **functions** of the **hypothalamus** is *to link* the **nervous system** *to* the **endocrine system** *via* the **pituitary gland (hypophysis)**.
- *Synthesizes* and *secretes* certain **neurohormones**, often *called* **Hypothalamic *releasing*** and ***inhibiting* hormones**, and these in turn ***stimulate*** or ***inhibit*** the **secretion** of **pituitary hormones**.

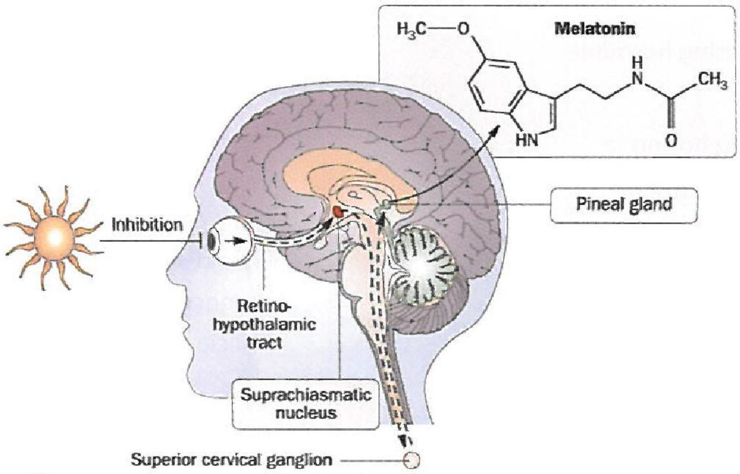
➢ Hypothalamic Hormones:-

Thyrotropin-releasing Hormone (TRH)	- *Stimulate* Thyroid-stimulating Hormone (TSH) *release from* **anterior pituitary**.
Dopamine (Prolactin-inhibiting Hormone; PIH)	- *Inhibit* Prolactin (PRL) *release from* **anterior pituitary**.
Growth Hormone-releasing Hormone (GHRH)	- *Stimulate* Growth Hormone (GH) *release from* **anterior pituitary**.
Somatostatin (SS) (Growth Hormone-Inhibiting Hormone; GHIH)	- *Inhibit* Growth Hormone (GH) *release from* **anterior pituitary**.
Gonadotropin-releasing Hormone (GnRH)	- *Stimulates* Follicle-stimulating Hormone (FSH) and Luteinizing Hormone (LH) *release from* **anterior pituitary**.
Corticotropin-releasing Hormone (CRH)	- *Stimulates* Adrenocorticotropic Hormone (ACTH) *release from* **anterior pituitary**.
Oxytocin	- *Stimulates* **uterine muscle contractions** and **release** of **milk** by **mammary glands** (*stored* and *secreted* into **bloodstream** by **posterior pituitary**).
Vasopressin (Antidiuretic Hormone; ADH)	- **Stimulates water reabsorption** by **kidneys** (*stored* and *secreted* into **bloodstream** by **posterior pituitary**).


Hypothalamus
Thyrotropin-releasing hormone
Dopamine
Growth hormone-releasing hormone
Somatostatin
Gonadotropin-releasing hormone
Corticotropin-releasing hormone
Oxytocin
Vasopressin
Thyroid
Triiodothyronine
Thyroxine
Pineal gland
Melatonin
Pituitary Gland
Anterior pituitary
Growth hormone
Thyroid-stimulating hormone
Adrenocorticotropic hormone
Follicle-stimulating hormone
Luteinizing hormone
Prolactin
Intermediate pituitary
Melanocyte-stimulating hormone
Posterior pituitary
Oxytocin
Vasopressin
Oxytocin (stored)
Anti-diuretic hormone (stored)


Hypothalamus
Indirect Control through Release of Regulatory Hormones
Corticotropin-releasing hormone (CRH)
Thyrotropin-releasing hormone (TRH)
Growth hormone-releasing hormone (GH-RH)
Growth hormone-inhibiting hormone (GH-IH)
Prolactin-releasing factor (PRF)
Prolactin-inhibiting hormone (PIH)
Gonadotropin-releasing hormone (GnRH)
Direct Release of Hormones
Sensory stimulation
Osmoreceptor stimulation
Regulatory hormones are released into the hypophyseal portal system for delivery to the anterior lobe of the pituitary gland.
Adrenal cortex
Anterior lobe of pituitary gland
Posterior lobe of pituitary gland
ACTH
ADH
Kidneys
Adrenal glands
TSH
GH
OXT
Liver
PRL
FSH
LH
MSH
Thyroid gland
Somatomedins
Males: Smooth muscle in ductus deferens and prostate gland
Females: Uterine smooth muscle and mammary glands
Glucocorticoids (steroid hormones)
Melanocytes (uncertain significance in healthy adults)
Bone, muscle, other tissues
Mammary glands
Testes of male
Ovaries of female
Thyroid hormones
Inhibin
Testosterone
Estrogen
Progesterone
Inhibin

Pineal Gland

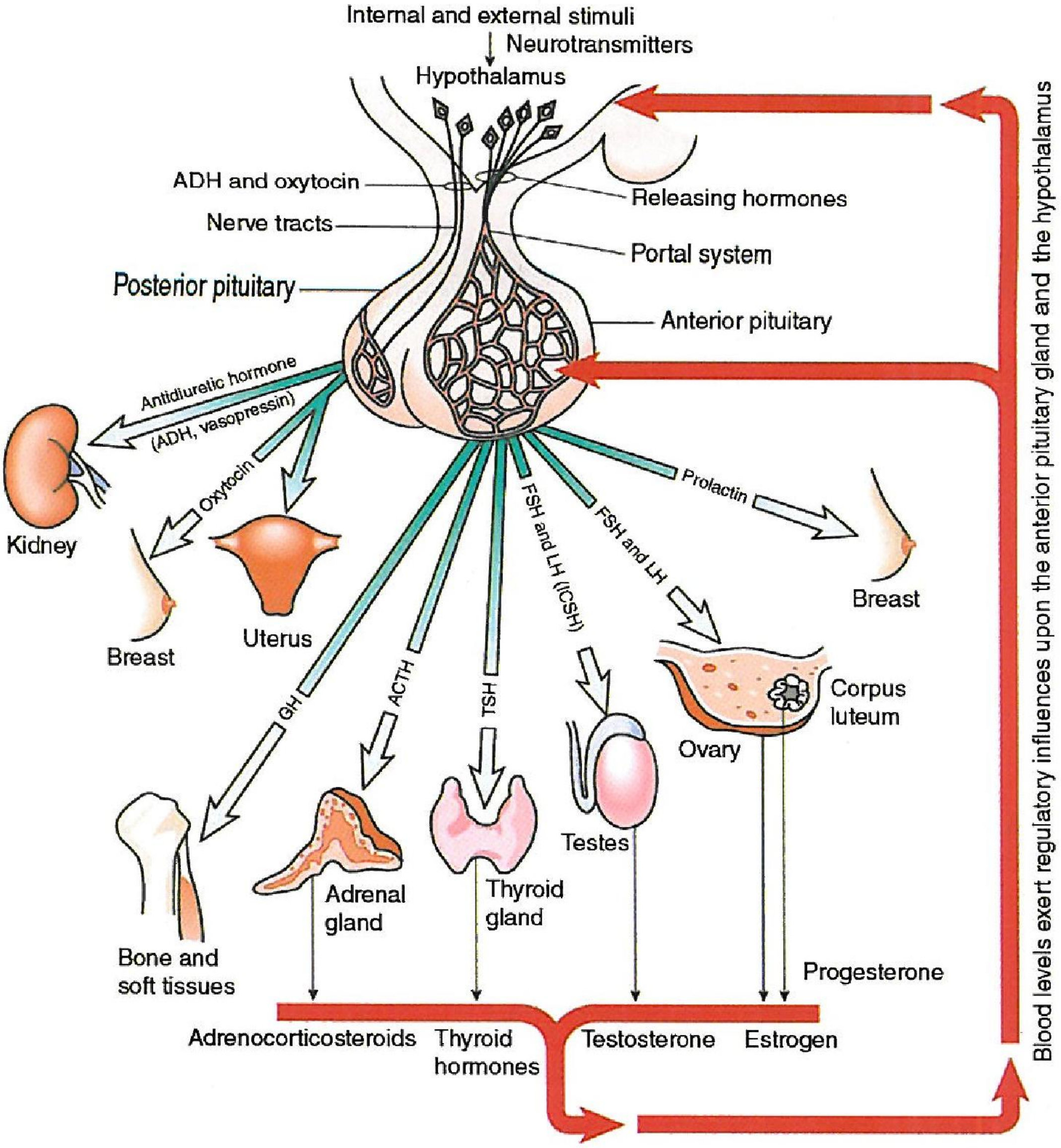

H_3C—O
Melatonin
H
N
CH_3
HN
O
Pineal gland
Inhibition
Retino-hypothalamic tract
Suprachiasmatic nucleus
Superior cervical ganglion

- **Pineal gland** is a *small* **endocrine gland** in the **brain**.
- The **pineal gland** ***produces*** **Melatonin hormone**, a **Serotonin** ***derived hormone*** which ***modulates*** **sleep patterns** in *both* **circadian** and **seasonal cycles**.

Hormones

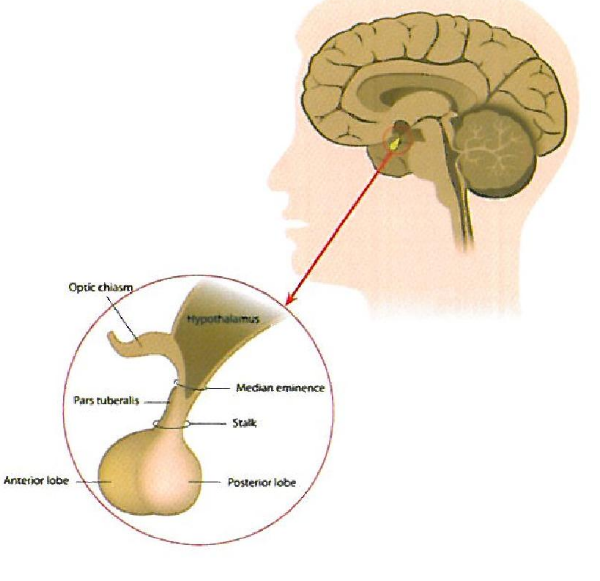
Endocrine Gland	Hormone Released	Chemical Class	Target Tissue/Organ	Major Function of Hormone
Hypothalamus	Hypothalamic Releasing and Inhibiting Hormones	Peptide	Anterior pituitary	Regulate anterior pituitary hormone.
Posterior Pituitary	Antidiuretic Hormone (ADH)	Peptide	Kidneys	Stimulates water reabsorption by kidneys
	Oxytocin	Peptide	Uterus, mammary glands	Stimulates uterine muscle contractions and release of milk by mammary glands.
Anterior Pituitary	Thyroid stimulating (TSH)	Glycoprotein	Thyroid	Stimulates thyroid.
	Adrenocorticotropic (ACTH)	Peptide	Adrenal cortex	Stimulates adrenal cortex.
	Gonadotropic (FSH, LH)	Glycoprotein	Gonads	Sex hormone production.
	Prolactin (PRL)	Protein	Mammary glands	Milk production.
	Growth Hormone (GH)	Protein	Soft tissue and bones	Cell division, protein synthesis and bone growth.
Thyroid	Thyroxine (T_4) and Triiodothyronine (T_3)	Iodinated amino acid	All tissue	Increase metabolic rate, regulates growth and development.
	Calcitonin	Peptide	Bones, kidneys & intestine	Lowers blood calcium level.
Parathyroids	Parathyroid (PTH)	Peptide	Bones, kidneys & intestine	Raises blood calcium level.
Adrenal Cortex	Glucocorticoids (Cortisol)	Steroid	All tissue	Increase blood glucose level and stimulates breakdown of protein.
	Mineralocorticoids (Aldosterone)	Steroid	Kidneys	Reabsorb sodium and excrete potassium.
	Sex Hormones	Steroid	Gonads, skin, muscles and bones	Stimulates reproductive organs and brings on sex characteristics.
Adrenal Medulla	Epinephrine and Norepinephrine	Modified amino acid	Cardiac and other muscles	Released in emergency situations, raises blood glucose level, "fight or flight" response.
Pancreas	Insulin	Protein	Liver, muscles, adipose tissue	Lowers blood glucose levels, promotes formation of glycogen.
	Glucagon	Protein	Liver, muscles, adipose tissue	Raises blood glucose levels.
Testes	Androgens (Testosterone)	Steroid	Gonads, skin, muscles and bone	Stimulates male sex characteristics.
Ovaries	Estrogen and Progesterone	Steroid	Gonads, skin, muscles and bones	Stimulates female sex characteristics.
Thymus	Thymosins	Peptide	T lymphocytes	Stimulates production and maturation of T lymphocytes.
Pineal Gland	Melatonin	Modified amino acid	Brain	Controls circadian and circannual rhythms.

Pituitary Hormones

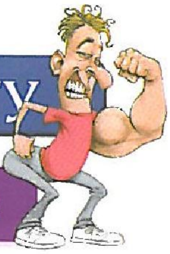

Internal and external stimuli
Neurotransmitters
Hypothalamus
ADH and oxytocin
Nerve tracts
Posterior pituitary
Releasing hormones
Portal system
Anterior pituitary
Antidiuretic hormone (ADH, vasopressin)
Kidney
Oxytocin
Breast
Uterus
GH
ACTH
TSH
FSH and LH (ICSH)
FSH and LH
Prolactin
Breast
Corpus luteum
Ovary
Testes
Bone and soft tissues
Adrenal gland
Thyroid gland
Progesterone
Adrenocorticosteroids
Thyroid hormones
Testosterone
Estrogen
Blood levels exert regulatory influences upon the anterior pituitary gland and the hypothalamus

➢ Pituitary Gland:-

- **Pituitary Gland** (or **Hypophysis**), is an **endocrine gland (master gland)** about the **size** of a **pea** and *weighing* **0.5 grams** in **humans**.
- It is **sits** in the ***sella turcica*** (small bony cavity) **off** the ***bottom*** of the **hypothalamus**.
- The **pituitary gland** has **3 parts**;
  1) **Anterior Pituitary** (**Adenohypophysis**); ***synthesizes** & **secretes*** **Thyroid Stimulating Hormone (TSH)**, **Adrenocorticotropic Hormone (ACTH)**, **Gonadotropic Hormones (FSH, LH)**, **Prolactin (PRL)** & **Growth Hormone (GH)**.
  2) **Intermediate Lobe**; ***synthesizes*** and ***secretes*** **Melanocyte-stimulating Hormones (MSH)**.
  3) **Posterior pituitary** (**Neurohypophysis**); ***store*** and ***secretes*** **Antidiuretic Hormone (ADH)** and **Oxytocin**.


Optic chiasm
Hypothalamus
Median eminence
Pars tuberalis
Stalk
Anterior lobe
Posterior lobe

Anterior Pituitary



Growth Hormone

- **Growth Hormone** is a *large* **polypeptide** (191-amino acid) that is ***released by*** **somatotropic cells** in the **anterior pituitary** in *response to* **Growth Hormone-releasing Hormone** *produced by* the **hypothalamus**.
- **Growth Hormone** is ***required*** during **childhood** and **adolescence** ***for attainment*** of ***normal*** **adult size** and has ***important*** **effects** *throughout* **postnatal life** on **lipid** and **carbohydrate *metabolism***, and on **lean body mass** and **bone density**.
- A ***recombinant*** *form* of ***human*** **Growth Hormone** *called* **Somatotropin** is **used** to ***treat*** **children's growth disorders** and **adult growth hormone *deficiency***.

Normal Values

- ***Random serum level*** (Medscape);

Men	< 5 ng/mL	Women	< 10 ng/mL
Children	0-20 ng/mL	Newborns	5-40 ng/mL

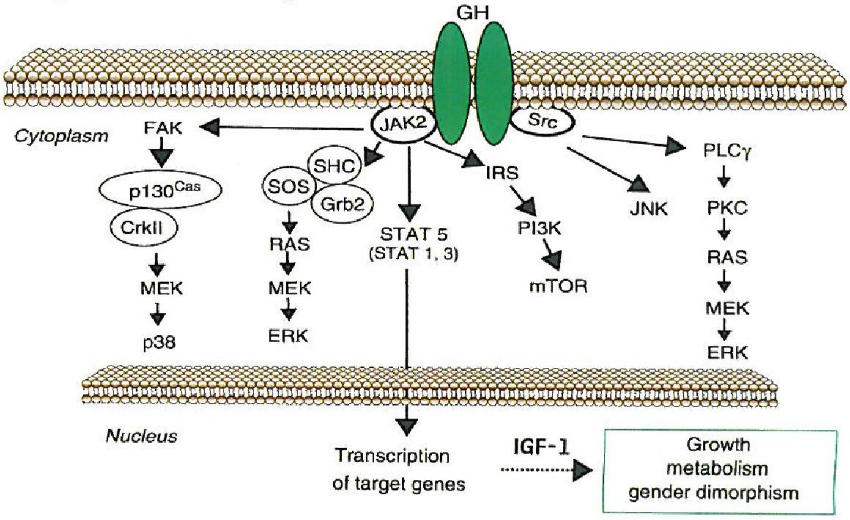
- **GH *suppression test*** (using 100 g glucose); < 0-2 ng/mL or undetectable.
- The ***largest*** **GH peaks** *occurs* about an **hour *after*** onset of **sleep**.
- With ***increasing*** **age**, **GH secretion *decreases***.

Regulation

- ***Stimulators*** of **GH *secretion***;
  - **Growth Hormone-*releasing* Hormone; GHRH (Somatocrinin)**.
  - **Ghrelin (hunger hormone)** via ***binding*** to **growth hormone secretagogue receptor (GHS-R)**.
  - **Deep sleep, fasting, hypoglycemia** and ***vigorous*** **exercise**.
  - **Sex hormones**.
  - **Arginine, Clonidine, L-DOPA, Nicotine** and **Niacin (Vitamin B_3)**.
- ***Inhibitors*** of **GH *secretion***;
  - **Growth Hormone-*inhibiting* Hormone; GHIH (Somatostatin)**.
  - ***Circulating*** **concentrations** of **GH** & **Insulin-like Growth Factor-1 (IGF-1)** *via* ***negative*** **feedback** on **pituitary** and **hypothalamus**.
  - **Glucocorticoids** and **hyperglycemia**.

Mechanism OF Action

- **One single *molecule*** of **GH *binding*** to **two GH receptors (GHR)** → ***dimerization*** of **GHR** → ***activates*** **signaling cascades** *mediated by* **receptor-associated JAK tyrosine kinases** and **STAT** (Signal Transducer and Activator of Transcription) → ***activate*** a ***variety*** of **signaling molecules** → ***increase*** in the ***production*** of **Insulin-like Growth Factor 1 (IGF-1) (Somatomedin C)** [similar in molecular structure to insulin].
- **IGF-1** is *produced* **primarily** in the **liver** and also *produced* in **bone, cartilage, muscle, kidney** and **other tissues**.



Function

Effect on Growth

- ***Increase*** **protein synthesis** and **cell division** → ***Increase*** **number** and **size** of **cell** → ***Increase*** **size** of **tissue** and **organs**.
- ***Effect on bone***;
  - **A)** ***Before*** and ***during*** **puberty** (before union of epiphysis);
    - ***Effect*** *on* **Chondrocytes** (cells found in healthy cartilage) → ***increase*** **linear growth** of **bone**.
    - ***Effect*** *on* **Osteoblasts** (cells responsible *for* bone formation) → ***increase*** **thickness** of **bone**.
  - **B)** ***After*** **puberty** (after union of epiphysis) → ***increase*** **thickness** of **bone**.

Effect on Metabolism

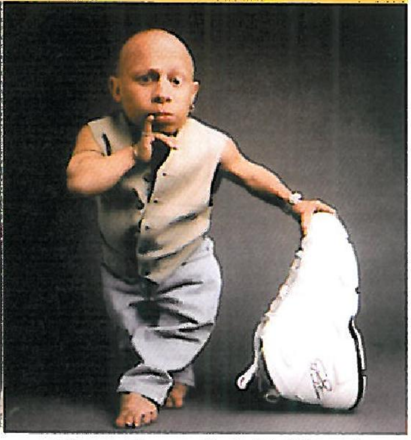
- **Protein** ***metabolism*** (**Anabolic effect**);
  - ***Increase*** **amino acids** ***uptake*** and ***transport*** *into* the **cells**.
  - ***Increase*** **DNA transcription** → ***m*****RNA** → ***Increase*** **protein synthesis**.
  - ***Decrease*** **protein** ***catabolism***.
- **Carbohydrate** ***metabolism*** (**Diabetogenic effect**; **Insulin-antagonistic**);
  - ***Increase*** **glucose** ***production*** by the **liver** (**Glycogenolysis**).
  - ***Increase*** **insulin resistance** *via* ***increase*** **free fatty acids (FFA)** ***flux*** *from* the **adipose tissue** → ***impaired*** **insulin** ***action*** at **target tissues**.
  - ***Suppress*** **glucose** ***uptake*** in the **muscle** and **adipose tissue**.
- **Fat metabolism**;
  - ***Increase*** **lipolysis** (breakdown of lipids into free fatty acids; FFA).
  - ***Increase*** **triglyceride** ***uptake*** in **liver** by ***enhancing*** **lipoprotein lipase**.

Disturbance of Growth Hormone Function

A) Hypofunction (Dwarfism)

- **Dwarfism**; **Adult height** of ***less than*** **147cm**; ***decrease*** **size** of the **trunk** and ***all*** **extremities**.
- **Achondroplasia** (genetic disorder) is the ***most common*** form of **dwarfism** (about 75% of dwarfism cases); the **arms** and **legs** are ***short***, while the **torso** is ***typically*** of **normal length**.
- **Achondroplasia** is due to a ***mutation*** in the **fibroblast growth factor receptor 3 (FGFR3)** ***gene*** (in normal development FGFR3 has a negative regulatory effect on bone growth).

Dylan Mark Postl (height; 1.35 m)



Verne Troyer (height; 81 cm)

- ***Treatments***; ***depends*** on the **underlying cause**;
  - **Growth Hormone** ***supplementation*** (**Somatotropin**);
    - *For* **children** *with* **dwarfism**; most cases, children receive **daily** ***injections*** for **several years** ***until*** they **reach** a *maximum* **adult** ***height*** (within the average adult range for their family).
    - *For* **children** *with* **achondroplasia**; **GH** ***does*** ***not*** ***increase*** **final adult** ***height***.
  - ***Other therapies***; **Surgical treatments**.

Somatotropin (Humatrope®) (Norditropin®) (Genotropin®)

- **Somatotropin** [soe-ma-TROE-pin] is a **recombinant** ***human*** **Growth Hormone**, is *administered by* **SC** or **IM** ***injection***.

Therapeutic Uses

- **Growth Hormone** ***Deficiency***.
- **Short-bowel Syndrome**.
- **HIV**-***associated*** **Wasting** or **Cachexia**.
- ***Off-label***; - **Enhance performance** by **athletes**.
  - *As* **Anti-aging Hormone** in **anti-aging programs**.

Mecasermin (Increlex®)

Mecasermin Rinfabate (Iplex®)

- **Mecasermin** [meh-KAZ-er-men] is a ***recombinant human*** **Insulin-like Growth Factor-1** (***rh*IGF-1**).
- **Mecasermin Rinfabate** [meh-KAZ-er-men RIN-fa-bayt] is a ***combination*** of ***rh*IGF-1** and **insulin-like growth factor binding protein-3** (**IGFBP-3**). **IGFBP-3** ***serves*** to ***prolong*** the **action** of **IGF-1**.
- ***Uses***; ***Long-term*** **treatment** of **growth failure** in ***children*** with ***severe*** **primary IGF-1 deficiency** (***Primary*** **IGFD**) or *with* **GH gene *deletion*** or **GH *insensitivity*** (Laron syndrome).
- ***Most common* Side Effects**; **hypoglycemia** (carbohydrate-containing meal or snack 20 minutes before or after Mecasermin administration is recommended).

B) Hyperfunction

Acromegaly

Maurice Tillet (1903-1954); Real Shrek

- **Acromegaly**; ***increase*** **GH** ***secretion after*** **puberty** (*after* union of epiphysis), *most common cases* is due to a **benign tumor** of **pituitary** (**pituitary adenoma**).
- ***No*** **linear growth** of **bone**, but ***increase*** **thickness** of **bone**; ***enlarged*** **extremities** & **face**
- **Acromegaly** is *derived from* the **Greek words akros "extremities"** and **megalos "large"**.
- ***Symptoms***; ***enlarged*** **hands** and **feet**, **thicker skin**, **hyperprolactinemia**, **arthritis**, **deepening voice**, **headaches**, & **vision problems**.

Gigantism

Robert Wadlow (1918-1940), the tallest man 2.72 m with his father, Harold Wadlow 1.82 m

- **Gigantism**; ***increase*** **GH** ***secretion before*** **puberty** (*before* union of epiphysis), *most common cases* is due to a **benign tumor** of **pituitary** (**pituitary adenoma**).
- **Linear growth** of **bone**, **symmetrical *over growth*** of **soft tissues** and **skeleton**.
- **Gigantism** is *derived from* the **Greek words gigas, "giant"**; **growth** & **height** ***above*** **average**.
- ***Symptoms***; ***enlarged*** **skeleton**, **muscles** and **organs**, **arthritis**, **deepening voice**, **headaches**, and **vision problems**.

- ***Treatment options***; **surgical *removal*** of the **tumor**, **drug *therapy*** (**GH antagonists**; *see next*) and **radiation *therapy*** of the **pituitary**.

Growth Hormone Antagonists

Somatostatin Analogs

- **Somatostatin** (**SST**) or **Growth Hormone-*inhibiting* Hormone** (**GHIH**) a **peptide hormone** (**14-amino-acid**), is ***found in*** the **hypothalamus**, *other parts* of **CNS**, **pancreas**, and *other sites* in **GIT**.
- It **functions** ***primarily*** as an ***inhibitory*** **paracrine factor** (cell-*to*-cell communication) and ***inhibits*** the ***release*** of **GH**, **TSH**, **Glucagon**, **Insulin** and **Gastrin**.
- **Somatostatin** has ***limited*** **therapeutic usefulness** *because* of its ***ultra-short*** **duration** of **action** (half-life; 1–3 minutes) and ***multiple*** **effects** in ***many*** **secretory systems**.
- ***Longer-acting*** **Somatostatin Analogs** *have been* **developed**.

Octreotide (Sandostatin®)

- **Octreotide** [ok-TREE-oh-tide] is a ***synthetic analogs*** of **Somatostatin**.
- It is the ***most widely*** **used** **somatostatin analog**, is **45 times** ***more potent*** than **Somatostatin** in ***inhibiting*** **GH** ***release*** but **only** ***twice*** as **potent** in ***reducing*** **Insulin** ***secretion***.
- ***Half-life***; *about* **80 minutes** (**30 times** ***longer*** *than* that of **Somatostatin**).
- ***Uses***; - **Acromegaly**.
    - **Carcinoid Tumors** (inhibits severe diarrhea and flushing episodes).
    - **Vasoactive Intestinal Peptide Tumors** (inhibits profuse watery diarrhea).
- ***Off-label uses***; *Usually*; 50–200mcg SC every 8 hours (Esophageal Variceal Bleeding; IV bolus *then* infusion).
    - **Esophageal variceal bleeding**.
    - **AIDS-Related Diarrhea**.
    - **Chemotherapy-Related Diarrhea**.
    - **Chylothorax**.
    - **GI** or **Pancreatic Fistula**.
    - **Ileostomy-Related Diarrhea**.
    - **Dumping Syndrome**.
    - **Neuroendocrine Tumors**.
- **Depot** ***formulations*** are **available** (**Sandostatin® LAR Depot**), allowing for ***administration*** **once** ***every*** **4 weeks**.
- **Vitamin B_{12}** ***deficiency*** *may* **occur** with ***long-term*** **use** of **Octreotide**.
- ***Side effects***; - **Gallbladder** ***problems*** (reduction of bile production and gallbladder contractility, which leads to increased viscosity of bile and increased incidence of gallstones), **Dysglycemia** (hyper or hypo), **Hypothyroidism** and **Bradycardia**.
    - **Nausea/vomiting, abdominal cramps & steatorrhea** *with* **bulky bowel movements**.

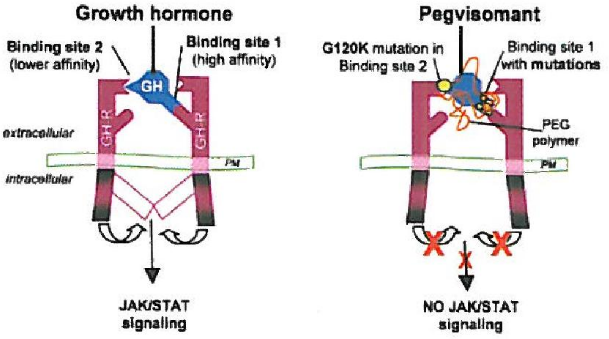
Lanreotide (Somatuline® Depot)

- **Lanreotide** [lan-REE-oh-tide] is a ***synthetic analogs*** of **Somatostatin**.
- **Lanreotide** ***reducing*** **GH** and ***normalizing*** **IGF-1** ***levels*** (**Octreotide** ***decrease*** **GH** and **IGF-1** ***levels***)
- ***Half-life***; **23** to **30 days** (**Usually dose**; 90-120 mg SC *every* 4 Week).
- ***Uses***; **Acromegaly** and **Gastroenteropancreatic Neuroendocrine Tumors**.
- ***Side effects***; *Like* **Octreotide**.

Growth Hormone Receptor Antagonists

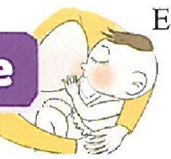
Pegvisomant (Somavert®)

- **Pegvisomant** [peg-VI-soe-mant] is a **GH** ***receptor antagonist*** used in the ***treatment*** of **acromegaly**.
- ***Mechanism of Action***; It is the **polyethylene glycol** (**PEG**) ***derivative*** of a ***mutant*** **GH**, *Like* ***native*** **GH**, **Pegvisomant** has ***two*** **GH** ***receptor*** **binding sites**. However, **one** of its **GH** ***receptor*** **binding sites** has ***increased*** **affinity** for the **GH** ***receptor***, whereas its ***second*** **GH** ***receptor*** **binding site** has ***reduced*** **affinity**. This ***differential*** **receptor affinity** ***allows*** the **initial step** (**GH** ***receptor*** **dimerization**) ***but blocks*** the **conformational changes** *required for* **signal transduction**.


Growth hormone
Binding site 2 (lower affinity)
Binding site 1 (high affinity)
GH
GH-R
GH-R
extracellular
intracellular
PM
JAK/STAT signaling
Pegvisomant
G120K mutation in Binding site 2
Binding site 1 with mutations
PEG polymer
PM
NO JAK/STAT signaling

- ***Dose***; ***initial***; 40 mg SC - ***maintenance***; 10-30 mg by SC daily.

Prolactin (PRL) Hormone



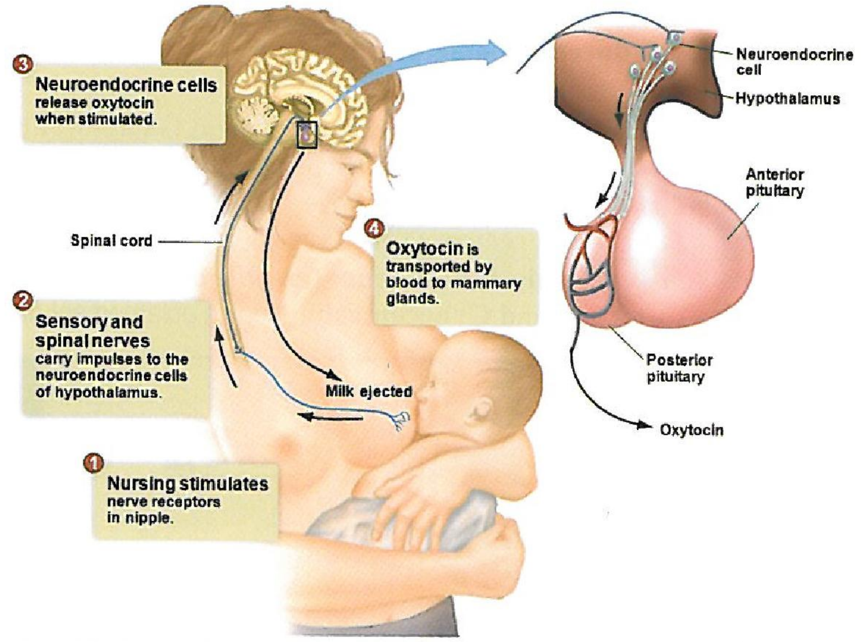
- **Prolactin** (**PRL**) is a **198-amino-acid** *peptide* **hormone** *produced* in the *anterior* **pituitary**.
- Its **structure** *resembles* that of **GH**.
- **Prolactin hormone** is *responsible for* **lactation** (**milk** *production* is *stimulated by* **Prolactin**).

Normal Values

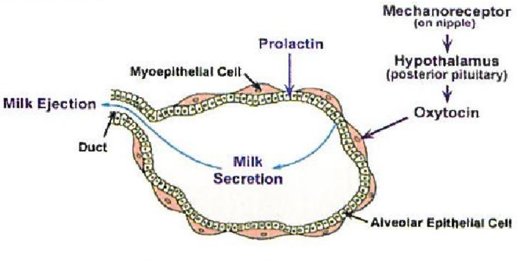
- *Reference Range* (Medscape);

Female		Male
Non-pregnant/Non-lactating;	2-29 ng/mL	2-18 ng/mL
Pregnant (third trimester)	10-209 ng/mL	

- **Milk Ejection Reflex**;
  - The **neuroendocrine** *reflex* in which an **infant** *suckling* at the **nipple** → **sensory stimulus** *routed to* the **hypothalamus** *causing*;
    1) **Oxytocin** *release* from the *posterior* **pituitary** *causes* **mammary gland muscles** *contraction* and *ejection* of **milk** *from* the **breast**.
    2) **Prolactin** *release* to *maintaining* the **ability** to **lactate**.


③ Neuroendocrine cells release oxytocin when stimulated.
Spinal cord
② Sensory and spinal nerves carry impulses to the neuroendocrine cells of hypothalamus.
① Nursing stimulates nerve receptors in nipple.
④ Oxytocin is transported by blood to mammary glands.
Milk ejected
Neuroendocrine cell
Hypothalamus
Anterior pituitary
Posterior pituitary
Oxytocin

- *Mechanism of Action*; *Like* **GH** (*One* **PRL** *binding* to *two* **PRL** *receptors* → *activation* of **JAK-STAT pathway** → *activate* a *variety* of signaling.
- **Prolactin** is *primary* **function** is to *stimulate* and *maintain* **lactation**. In addition, it *decreases* **sexual drive** and **reproductive function**.
- **Prolactin** *secretion* is *inhibited* by **Dopamine** *acting at* D_2 **receptors**.


Mechanoreceptor
(on nipple)
Hypothalamus
(posterior pituitary)
Oxytocin
Prolactin
Myoepithelial Cell
Milk Ejection
Duct
Milk Secretion
Alveolar Epithelial Cell

Alveolus of Mammary Gland

Regulation

- *Stimulators* of **Prolactin** *secretion*;
  - **Dopamine antagonists** (*such as* **Chlorpromazine**).
- *Inhibitors* of **Prolactin** *secretion*;
  - **Dopamine** (**Prolactin-inhibiting Hormone**; **PIH**).
  - **Dopamine agonists** (**Bromocriptine** and **Cabergoline**).
  - *Circulating* **concentrations** of **Prolactin** *via negative* **feedback** on **pituitary** and **hypothalamus**.

Function

Female

- *Stimulate* and *maintain* **milk** *secretion*.
- *During* **pregnancy** cause *enlargement* of the **mammary glands** and *prepare* for **milk** *production*.
- *Inhibit* **ovulation** (*due to suppress* **gonadotrophic hormone release** → *decrease* **estrogen** → **infertility** and **amenorrhea** *during* **lactation**.

Male

- *Specific* **function** of **prolactin** in men is *not well*-known.

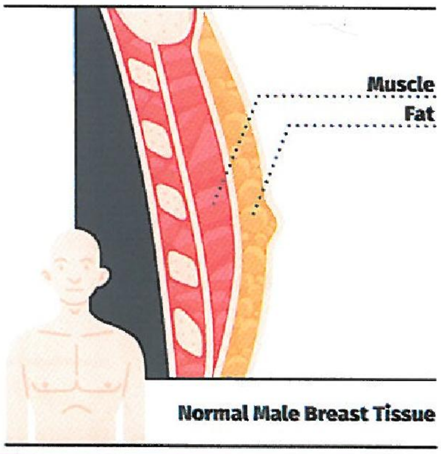
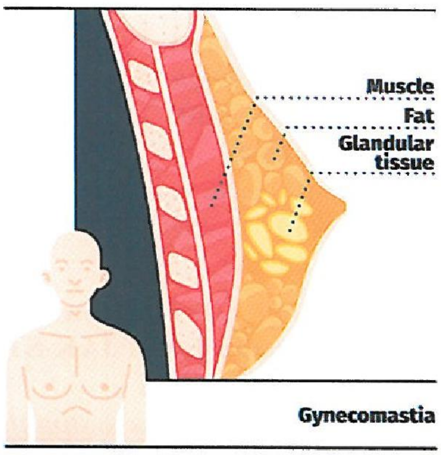
Disturbance of Prolactin Function

Hypoprolactinemia

- **Hypoprolactinemia** is a **medical condition** *characterized by* ***serum*** **Prolactin levels** ***below*** *than* **normal** (*serum* **Prolactin** *deficiency*), it is *very rare* **condition** and ***commonly*** *associated with* **anterior pituitary** ***dysfunction***.
- In **women** cause **lactation failure** ***after*** **childbirth**.
- There are ***no treatments*** which ***increase*** **Prolactin** ***levels*** in **humans** (No preparation of prolactin).

Hyperprolactinemia

- **Hyperprolactinemia** is the *presence* of **abnormally** ***high*** **levels** of **Prolactin** in the **blood**.
- *Causes*;
  - ***More*** **commonly** *associated with* **Prolactin-*secreting*** **adenomas**.
  - **Physiological** (*non-pathological*); **Pregnancy**, **breastfeeding** and **mental stress**.
  - **Drug-induced hypersecretion**; **Dopamine antagonists** (*such as* **Chlorpromazine**).
- *Symptoms*;

Female	- **Oligomenorrhea** or **Amenorrhea** and **Galactorrhea**. - ***Inhibit*** **ovulation**; due to hypogonadism (↓ gonadotrophic hormone; FSH & LH) → infertility. - ***Loss of*** **libido**; loss of sex drive. - ***Painful*** **intercourse**; due to vaginal dryness due to ↓ estrogen.
Male	- ***Loss of*** **libido** & **Impotence** (***erectile*** **dysfunction**); due to hypogonadism (↓ testosterone). - **Infertility** and **Gynecomastia**; benign enlargement of breast tissue in males.  Normal Male Breast Tissue  Gynecomastia

Dopamine Agonists

Bromocriptine (Lactodel®) (Parlodel®)	**Cabergoline** (Dostinex®)

- **Bromocriptine** [broe-moe-KRIP-teen] is an **ergot *derivative***, is **used** in the ***treatment*** of **Parkinson's disease**, **Hyperprolactinaemia**, **Neuroleptic Malignant Syndrome** (**NMS**) and **Type 2 Diabetes** (Quick-release formulation of Bromocriptine (Cycloset®) given once in the morning, is believed to reset the circadian clock as in a winter rhythm; ↑ dopaminergic neuron activity in morning lead to ↑ glucose tolerance).
- **Cabergoline** [ca-BER-goe-leen] is a ***long-acting*** **dopamine agonist** with a ***high affinity*** for **D_2 receptors**, is **used** in **Hyperprolactinaemia**.
- **Quinagolide** is a ***non-ergot*** with ***high*** **D_2** ***affinity*** *approved in* **Europe** for **Hyperprolactinaemia**.
- *Doses* for **Hyperprolactinaemia**;

Bromocriptine	- **Initial**: 1.25-2.5 mg orally daily. **Titration**: Add 2.5 mg orally, as tolerated, every 2-7 days. - **Maintenance**: 2.5-15 mg daily.
Cabergoline	- ***Prevent*** **lactation**; **1 mg (2 tablets)** on the **first day** ***after*** **delivery**. - **Stop lactation** ***after*** **breast-feed**; **0.25 mg (1/2 tablet)** ***every*** **12 hours** *for* **two days**. - ***Reduce*** **prolactin levels** in ***other*** **conditions**; **0.5 mg/week** ***spread out*** **over a week** (e.g. 1/2 tablet on Monday and the other 1/2 of the tablet on Thursday).

- *Common Side Effects*; **drowsiness**, **nausea**, **headache**, **dizziness** and **vertigo**.
- **Bromocriptine** and *other* **ergot *derivatives***, used with **caution** in **patients** with ***history*** of **myocardial infarction** or **peripheral vascular disease**.

Adrenocorticotropic Hormone (ACTH)

- **Adrenocorticotropic Hormone** (**ACTH**) or **Adrenocorticotropin** or **Corticotropin** is a ***polypeptide*** **hormone** (**39 amino acids**) ***produced*** and ***secreted*** by **Corticotroph cells** in the **anterior pituitary** in *response to* **Corticotropin-releasing Hormone** (**CRH**) from the **hypothalamus**.
- **ACTH** increased ***production*** and ***release*** of **Cortisol** by the **cortex** of the **adrenal gland**.
- **ACTH** ***acts*** by ***binding*** to **cell surface ACTH receptors** (**G protein-coupled receptor** via increase in intracellular **cAMP** and subsequent activation of protein kinase).

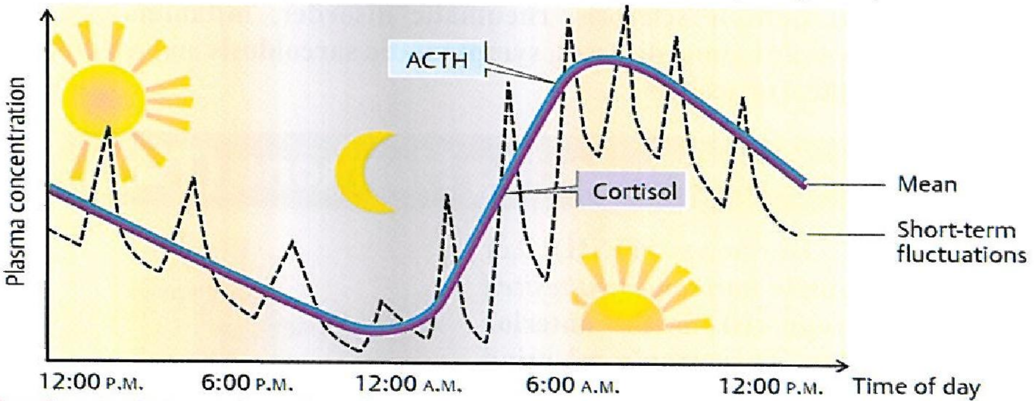
Normal Values

- ***Reference Range*** of ***Morning Levels*** of **ACTH** (Medscape);

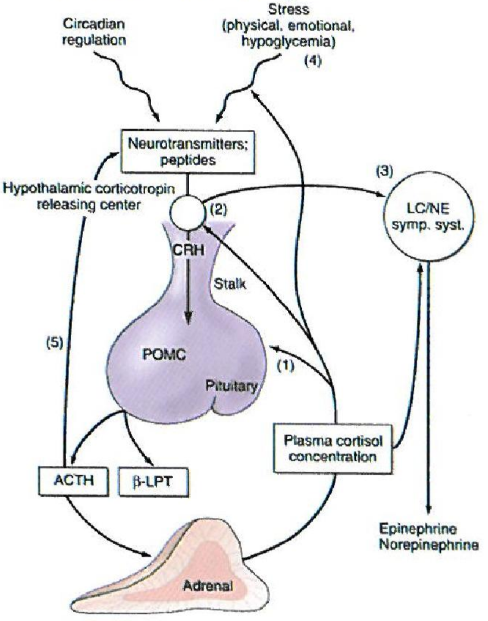
Adults		Children	
Female	5-27 pg/mL	Prepubertal	7-28 pg/mL
Male	7-50 pg/mL	Postpubertal	2-49 pg/mL

Each laboratory has its own reference range depending on the assay used

- ***Plasma*** **ACTH** & **Cortisol** *levels* ***exhibit*** ↑ **peaks** (**6-8 AM**) & ↓ **nadirs** (**11 PM**).
- **ACTH levels** are ***higher*** in **men** and ***during*** **pregnancy**.

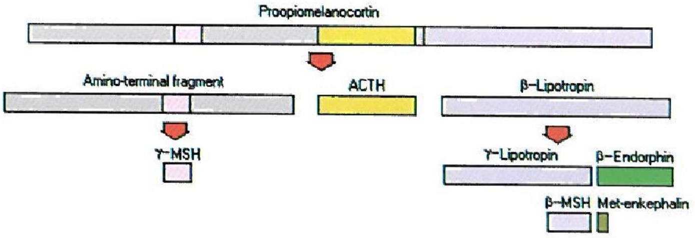


- **Hypothalamic-pituitary-adrenal axis**;



Circadian regulation
Stress (physical, emotional, hypoglycemia)
(4)
Neurotransmitters; peptides
Hypothalamic corticotropin releasing center
(2)
(3)
LC/NE symp. syst.
CRH
Stalk
(5)
POMC
(1)
Pituitary
Plasma cortisol concentration
ACTH
β-LPT
Epinephrine
Norepinephrine
Adrenal

  - ***Biological*** **stress** and **circadian rhythm** are the ***most important*** **regulatory mechanisms** in **hypothalamic-pituitary-adrenal axis**.
  - **Stress** and *during* **circadian regulation** → ***activation*** of ***neurosecretory*** **CRH** *from* the **hypothalamus** → ***stimulate*** **ACTH** ***release*** *from* the **anterior pituitary** → ***stimulates*** the ***secretion*** of **Glucocorticoids** from the **adrenal cortex**.
  - **CRH** is ***responsible*** for the ***synthesis*** and ***release*** of the ***peptide*** **Proopiomelanocortin** (**POMC**) by the **hypothalamus**.
  - ***Within*** the **pituitary gland**, **ACTH** is ***produced*** in a ***process*** that also ***generates*** several other hormones called **Proopiomelanocortin** (**POMC** "**Big Mama**") is ***synthesized*** and ***proteolytically*** **chopped** into ***several*** **fragments**.
  - The ***major attributes*** **hormones** (*other than* **ACTH**) that are ***produced*** in this process;



Proopiomelanocortin
Amino-terminal fragment
ACTH
β-Lipotropin
γ-MSH
γ-Lipotropin
β-Endorphin
β-MSH
Met-enkephalin

    - **Lipotropin**: its major importance is as the precursor to beta-endorphin.
    - **Beta-endorphin** and **Met-enkephalin**: Opioid peptides.
    - **Melanocyte-stimulating hormone** (**MSH**): Control melanin pigmentation in the skin.
- **Hypercortisolism** is ↑↑ **secretion** of **Corticosteroids** (*seen in* **Cushing's syndrome**) and **Hypocortisolism** is ↓↓ **secretion** of **Corticosteroids** (*seen in* **Addison's Syndrome**); *see Adrenocortical Hormones topic*.

Synthetic ACTH

Cosyntropin or **Tetracosactide** (Synacthen®) - **Tetracosactide Acetate** (Synacthen® Depot)

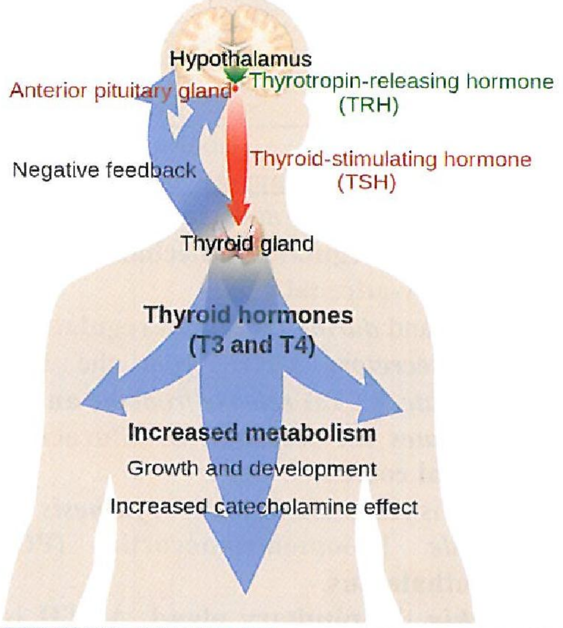
- **Cosyntropin** [koe-sin-TROE-pin] is a ***synthetic derivative*** of **ACTH**.
- It is **contains *only*** the ***first* 24** (of a total 39) **amino acids** of **ACTH** *but* **retains *full* function**.
- **Cosyntropin** use as ***diagnostic agent*** in **adrenocortical insufficiency** (**ACTH stimulation test**); ***differentiating* between *primary* adrenal insufficiency** (Addison's disease which adrenal glands do not produce sufficient glucocorticoids and mineralocorticoids) and ***secondary* adrenal insufficiency** (caused by the inadequate secretion of ACTH by the pituitary); ***Primary* adrenal insufficiency *cannot*** be ***stimulated*** by **ACTH** where a ***secondary* adrenal insufficiency** will ***respond*** to ***adequate*** **stimulation** with **ACTH**.
- *Dose*; 0.25-0.75 mg IM or IV over 2 minutes.
- **Cosyntropin *can*** be **used** in ***short-term*** **therapy** in ***conditions for*** which **Glucocorticoids** are ***usually* used** such as **rheumatic diseases**.

Repository Corticotropin Injection (HP Acthar® Gel)

- **Repository Corticotropin Injection** is a ***highly*** **purified Adrenocorticotropic hormone** (**ACTH**).
- It is ***stimulates*** **adrenal cortex** to ***secrete*** **Cortisol**, **Corticosterone** and **Aldosterone**.
- *Uses*; **Infantile spasms**, **multiple sclerosis**, **rheumatic disorder**, **inflammatory dermatologic diseases**, **inflammatory ophthalmic diseases**, **symptomatic sarcoidosis** and **edematous state**.
- *Side effects*: *similar to* **Glucocorticoids**.

Thyroid-Stimulating Hormone (TSH)

- **Thyroid-stimulating Hormone** (**TSH**) or **Thyrotropin** is a ***glycoprotein hormone synthesized*** and ***secreted*** by **thyrotrope cells** in the **anterior pituitary**, in *response to* **Thyrotropin-releasing Hormone** (**TRH**) from the **hypothalamus**.
- **TSH *regulates*** the **endocrine function** of the **thyroid gland** to ***synthesize*** and ***release*** **Thyroxine** (T_4) and **Triiodothyronine** (T_3); the ***effects*** of T_3 **3-4 times *more* potent** than T_4.
- **Thyroglobulin** (**Tg**) is a **protein *produced by*** the **follicular cells** of the **thyroid gland** and is a ***precursor*** of the **thyroid hormones**.
- **Thyroglobulin concentration *increases*** in *both* **benign** (**Graves' disease**, ***subacute*** **thyroiditis**, **Hashimoto thyroiditis**) and **malignant *conditions*** (**thyroid adenoma**, **thyroid papillary** and **follicular cancer**).


Hypothalamus
Anterior pituitary gland
Thyrotropin-releasing hormone (TRH)
Negative feedback
Thyroid-stimulating hormone (TSH)
Thyroid gland
Thyroid hormones (T3 and T4)
Increased metabolism
Growth and development
Increased catecholamine effect

Normal Values

Pediatric Age (mIU/L)		Pregnancy (mIU/L)	Adult (mIU/L)
Premature; 28-36 wk; 1st wk	0.7-27.0	**1st trimester**: 0.3-4.5	**21-54 years**: 0.4-4.2
Birth to 4 days	1-39	**2nd trimester**: 0.5-4.6	**55-87 years**: 0.5-8.9
2-20 weeks	1.7-9.1		
21 weeks to 20 years	0.7-64	**3rd trimester**: 0.8-5.2	

R; Medscape; each laboratory has its own reference range depending on the assay used

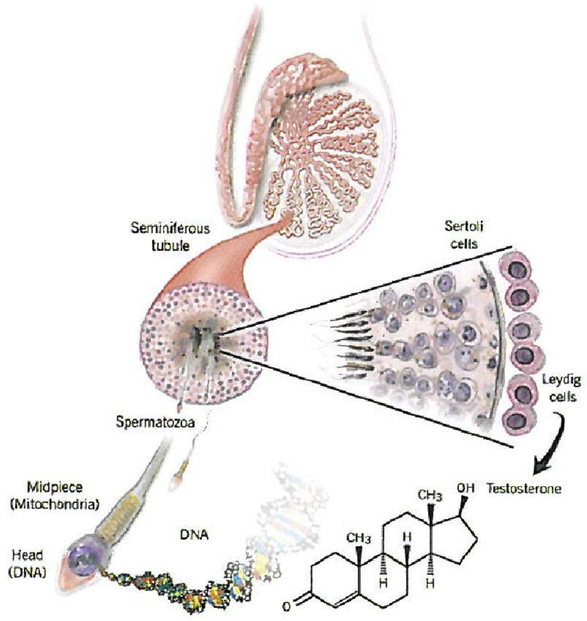
Synthetic TSH

Thyrotropin alfa (Thyrogen®)

- **Thyrotropin alfa** [thye-roe-TROH-pin AL-fa] is a ***recombinant*** **TSH**.
- *Uses*; as **adjunctive diagnostic tool** for ***serum*** **Thyroglobulin** (**Tg**) ***testing*** *with* or *without* **radioiodine imaging** in the *follow-up* of **patients** with ***well-differentiated*** **thyroid cancer** who have *previously* undergone **thyroidectomy**.

Gonadotropins

- **Gonadotropins** are ***glycoprotein* polypeptide hormones** *secreted by* **gonadotrope cells** of the **anterior pituitary** in ***response to*** **Gonadotropin-releasing hormone** (**GnRH**) from the **hypothalamus**.
- ***Mammalian*** **Gonadotropins** ***includes***;
  - **Follicle-stimulating Hormone** (**FSH**) and **Luteinizing Hormone** (**LH**); ***Produced*** *by* the **anterior pituitary** in **male** and **female**, they are ***act on*** the **gonads**, ***controlling*** **gamete** and **sex hormone** ***production***.
  - ***Human*** **Chorionic Gonadotropin** (**hCG**); ***Produced*** *by* the **placenta** ***after*** **implantation** in **pregnancy**, **hCG** is ***detected*** in **pregnancy tests**, **hCG** is ***nearly*** **identical** with **LH**; its ***actions*** are ***mediated through*** **LH** ***receptors***.
- **N.B.**;
  - ***Human*** **Menopausal Gonadotropin** (**hMG**) or **Menotropin**; is **one** of the **pharmaceutical gonadotropin preparations**, ***extracted*** *from* the **urine** of ***postmenopausal*** **women** and ***contains*** **FSH** and **LH**.
  - **Sertoli cell**: a kind of **sustentacular cell** which *serves as* a "**nurse**" **cell** of the **testes** and which is ***part of*** a **seminiferous tubule**.
  - **Leydig cell**: one of the **interstitial cells**, ***located*** **next** to the **seminiferous tubules** ***inside*** the **testicle** that ***produce*** **Testosterone**.
  - **Inhibin**: a ***peptide hormone***, secreted by the **gonads**, which ***inhibits*** the **secretion** of **FSH**.



Normal Values

Follicle-stimulating Hormone (FSH)	
Female	
0-7 years	<6.7 mIU/mL
> 8 years	Follicular: 3.1-7.9 mIU/mL Mid-cycle: 2.3-18.5 mIU/mL Luteal: 1.4-5.5 mIU/mL Postmenopausal: 30.6-106.3 mIU/mL
Male	
0-7 years	<6.7 mIU/mL
> 8 years	1.3-19.3 mIU/mL

Luteinizing Hormone (LH)	
Female	
Prepubertal	0-4.0 mIU/mL
Pubertal	0.3-31.0 mIU/mL
Premenopausal	Follicular: 1-18 mIU/dL Mid-cycle: 20-105 mIU/mL Luteal: 0.4-20.0 mIU/mL
Postmenopausal	15.0-62.0 mIU/mL
Male	
Prepubertal	0.3-6.0 mIU/mL
Adult	1.8-12.0 mIU/L

R; Medscape; each laboratory has its own reference range depending on method

Function

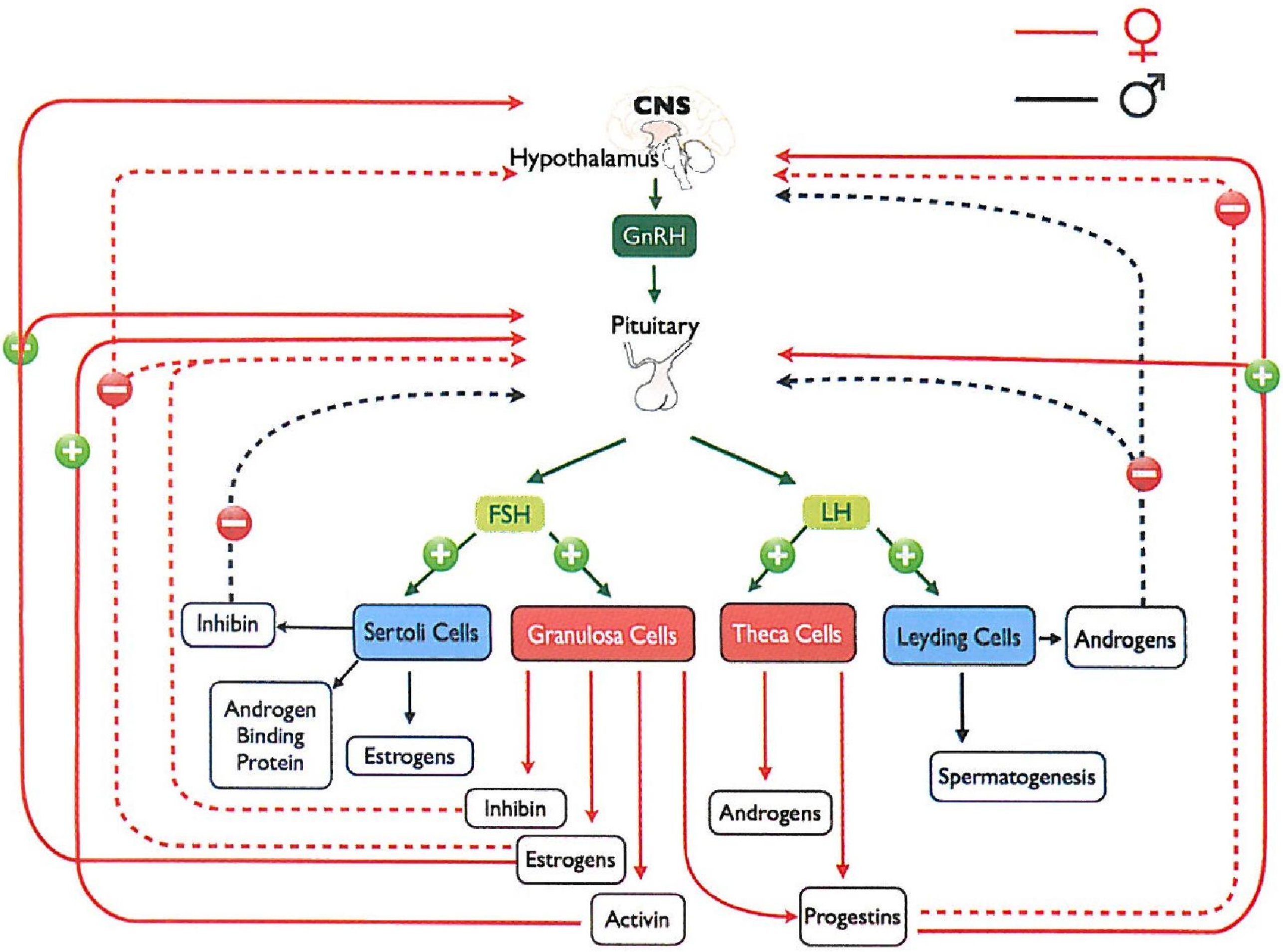
Male

- **FSH**;
  - ***Stimulates*** **spermatogenesis** (*primary function*).
  - ***Stimulates*** **Sertoli cells** to ***produce*** **androgen-binding protein (ABP)**;
    - ABP is binds specifically to androgen hormones (Testosterone and Dihydrotestosterone) and made less lipophilic hormones and become high concentrated within the luminal fluid of the seminiferous tubules. The higher levels of these hormones enable spermatogenesis.
  - ***Stimulates*** **Sertoli cells** to ***convert*** Testosterone to Estrogen that is also ***required for*** **spermatogenesis**.
- **LH**;
  - ***Stimulate*** **Leydig cells (interstitial cells)** to ***produce*** Testosterone.

Female

- **FSH**;
  - ***Stimulates*** the **growth** of ***immature*** **ovarian follicles** in the **ovary** to ***produce*** Estrogen.
  - ***Stimulates*** **Granulosa cells** to ***convert*** Androgens to Estrogen.
- **LH**;
  - ***Induces*** **ovulation**.
  - ***Development*** of the **corpus luteum** to ***produce*** Progesterone.
  - ***Stimulates*** **Theca cells** to ***produce*** Androgen in the **follicular** ***stage***.

Regulation


♀
♂
CNS
Hypothalamus
GnRH
Pituitary
FSH
LH
Inhibin
Sertoli Cells
Granulosa Cells
Theca Cells
Leyding Cells
Androgens
Androgen Binding Protein
Estrogens
Inhibin
Androgens
Spermatogenesis
Estrogens
Activin
Progestins

Disturbance of Gonadotropins Function

Hypergonadotropic

- **Hypergonadotropic hypergonadism**; ***high*** **gonadotropin** ***levels*** and ***high*** **gonadal** ***function***.
- **Hypergonadotropic hypogonadism**; ***inability*** of the **body** to **respond** to **FSH** and **LH**, lead to ***elevate*** **gonadotropin** ***levels*** (No negative feedback inhibition).
  - **Leydig cell hypoplasia**; ***inability*** of the **body** to **respond** to **LH** (**LH** ***insensitivity***).
  - **Ovarian follicle hypoplasia**; ***inability*** of the **body** to **respond** to **FSH** (**FSH** ***insensitivity***).

Hypogonadotropic

- **Hypogonadotropic hypogonadism**; ***deficiency*** of **Gonadotropins** due to **pituitary disease** results in **hypogonadism**, which *can lead to* **infertility**.

- ***All*** **gonadotropin preparations** are **pregnancy category X** *should be* **avoided** in pregnancy.
- **Caution**; ***during*** **hormone reconstitution**; **Do not shake**, but ***gently*** **swirl** until the **solution** is ***clear***.

FSH Preparations

Urofollitropin (Fertinex®) (Fostimon®)

Follitropin Alfa (Gonal-*f*®) (Epigonal®)

Follitropin Beta (Puregon®)

- **Urofollitropin** [yoor-oh-fol-li-TROE-pin] is a ***highly*** **purified FSH** ***extracted from*** the **urine** of **postmenopausal women**, while **Follitropin** [foe-li-TRO-pin] **Alfa** and **Beta** are ***human*** **recombinant FSH** ***preparations***.
- ***Recombinant*** **FSH** ***preparations*** (**rFSH**); ***More*** **pure** and ***more*** **easily administered**, ***but*** they are ***more*** **expensive**.
- **FSH** is ***required for*** *normal* **follicular growth, maturation, gonadal steroid production**, and **spermatogenesis**.
- ***Uses***; - **Assisted Reproductive Technology** (**ART**); *such as* **In Vitro Fertilization** (**IVF**).
  - **Ovulation** ***induction***: in women received **GnRH** ***agonist*** or ***antagonist*** for **pituitary suppression**.
  - **Spermatogenesis** ***induction*** (Gonal-*f*®).
- ***Dose***; **75-300 IU per day SC**.
- ***Common Side Effects***; **Headache** and **Ovarian Hyperstimulation Syndrome**; **OHSS** (severe pelvic pain, nausea, vomiting and weight gain).

LH Preparations

Lutropin Alfa (Luveris®)

- **Lutropin alfa** [LOO-troe-pin AL-fa] is the ***first*** and ***only recombinant*** form of ***human*** **LH**.
- ***Uses***; **Follicle Stimulation**; ***Only*** in ***combination with*** **Follitropin** ***until*** **follicular** ***maturation*** **occurs** in **female infertility**.
- ***Dose***; **75-300 IU per day SC**.
- ***Common Side Effects***; **Headache** and **OHSS**.

Other Gonadotropin Preparations

Human Menopausal Gonadotropins (hMG) or Menotropin (Pergonal®)

- **Human Menopausal Gonadotropins** (**hMG**) or **Menotropins** [men-oh-TROE-pins] are ***obtained from*** the **urine** of **menopausal women** and ***contains*** **FSH** and **LH**.
- ***Uses***; - **Assisted Reproductive Technology** (**ART**); such as **In Vitro Fertilization** (**IVF**);
    - Once adequate follicular development is evident, Human Chorionic Gonadotropins (hCG) should be administered one day following the last dose of Menotropins.
  - ***Infertility*** in **women** and **men**.
- ***Dose***; **IM** or **SC 75-150 IU** of **FSH** + **75-150 IU** of **LH** ***once*** a **day**.
- ***Common Side Effects***; **Headache**, **OHSS** and **multiple births**.

Human Chorionic Gonadotropin (hCG) (Pregnyl®)

- **Human Chorionic Gonadotropin (hCG)** *produced by* **human placenta** and *excreted into* the **urine**.
- It is a ***glycoprotein*** *composed of* an **alpha** and a **beta sub-unit**.
    - **α-subunit** (92 amino acids) **virtually *identical*** to that of **FSH**, **LH** and **TSH**.
    - **β-subunit** (145 amino acids) ***differ*** in **amino acid *sequence***.
- **Choriogonadotropin alfa (rhCG)** (Ovidrel®) is a ***recombinant*** form of **hCG**.
- ***Uses***; - **Prepubertal cryptorchidism**; ***induce*** **testicular descent**.
    - **Hypogonadotropic hypogonadism** (*secondary to* a pituitary deficiency) in **males**.
    - ***Induction*** of **ovulation** and **pregnancy**.
- ***Dose***; **IM *only*** **500-1000 units *3 times*** a **week**.
- ***Common Side Effects***; **Ovarian cyst**, **OHSS**, **abdominal pain**, **nausea**, **vomiting** and **injection** site **inflammation**.

GnRH and its Analogues

Gonadorelin (Factrel®)		
Leuprolide (Lupron®)	**Buserelin** (Suprefact®)	**Histrelin** (Vantas®)
Goserelin (Zoladex®)	**Nafarelin** (Synarel®)	**Triptorelin** (Decapeptyl®)

- **Gonadotropin-releasing hormone (GnRH)** is a **decapeptide** (10 amino acids) ***stimulates*** the ***synthesis*** and ***secretion*** of the **Gonadotropins**, **FSH** and **LH**.
- **Gonadorelin** [goe-nad-oh-RELL-in] is an ***acetate*** salt of ***synthetic human*** **GnRH**.
- **Leuprolide** [loo-PROE-lide], **Buserelin** [bue-se-REL-in], **Histrelin** [his-TREL-in], **Goserelin** [GOE-se-REL-in], **Nafarelin** [NAFF-a-rel-in] and **Triptorelin** [trip-toe-REL-in] are **GnRH analogues**. They are **effective** in ***suppressing*** **production** of the **Gonadotropins**; ***Initial*** **increase** in **FSH** and **LH** ***secretion*** → ***sustained*** **stimulation** of **GnRH receptors** → **hypogonadal effect** (***decrease*** **FSH** and **LH**); *due to* ***down-regulation***. ***Suppression*** of **Gonadotropins** → ***leads*** to ***reduced*** **production** of **gonadal steroid hormones** (**Androgens** and **Estrogens**).
- ***Pharmacokinetics***;
    - **Gonadorelin** ***administered*** **IV** or **SC**.
    - **GnRH analogues** can be ***administered*** **SC**, **IM**, **nasal spray** (**Nafarelin** & **Buserelin**) or **SC implant**.
    - ***Durations of action***; from ***several*** **hours** (daily administration) to **1**, **4**, **6**, or **12 months** (**depot forms**).
- **Gonadorelin**;
    - ***Very short*** **half-life** (IV = 4 min) and ***used*** as a **diagnostic agent** (assess pituitary gland function).
    - ***Unlike other*** **GnRH analogues**, it is ***not*** **used** to ***suppress*** **sex hormone *production***.
    - It is also ***used*** in the ***treatment*** of ***primary*** **hypothalamic amenorrhea**, **hypogonadotropic hypogonadism**, **delayed puberty**, **cryptorchidism** and **infertility**.
- **GnRH analogues**;
    - ***More*** **potent** and ***long*** **lasting** **used** to ***suppress*** **sex hormone *production***.
    - ***Uses***; **Prostate cancer**, **breast cancer**, **endometriosis**, **uterine fibroids** and **early puberty**.
    - **Triptorelin** is ***widely used*** in ***preparation for*** **In Vitro Fertilization (IVF)** ***undergoing controlled*** **ovarian hyperstimulation**.

Side Effects

- **Gonadorelin**; **headache**, **light-headedness**, **nausea** and **flushing**.
- **Hypersensitivity dermatitis** and **local swelling** can occurs at ***SC injection*** and **sinusitis** can occur in ***nasal spray***.
- ***Within*** the ***first*** **month** of **therapy**; **Ovarian cysts** *may* **develop** due to its **flare effect** on **gonadotropin secretion** and generally ***resolve*** after an additional 6 weeks.
- ***Long term*** **use** causes **typical symptoms** of **menopause** (**hot flushes**, **sweats** and **headaches**), **depression**, ***diminished*** **libido**, ***generalized*** **pain**, **osteoporosis** and **vaginal dryness**.

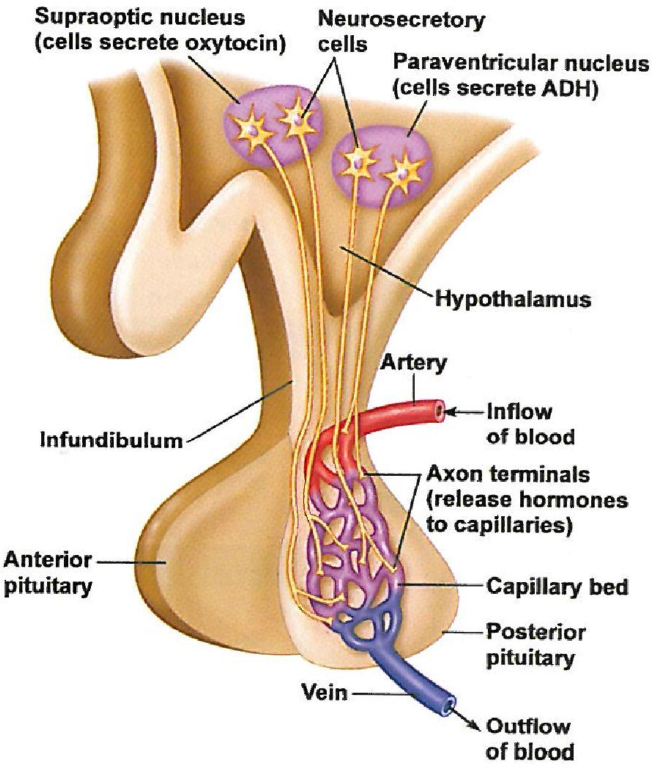
GnRH Receptor Antagonists

Cetrorelix (Cetrotide®)	**Ganirelix** (Orgalutran®)
Abarelix (Plenaxis®)	**Degarelix** (Firmagon®)

- **Cetrorelix** [set-roe-REL-iks], **Ganirelix** [GA-ni-REL-ix], **Abarelix** [ab-ah-REL-ix] and **Degarelix** [DEG-a-REL-ix] are **GnRH receptor antagonists**.
- They are ***inhibit*** the ***secretion*** of **FSH** and **LH** in a ***dose-dependent*** manner.
- ***Uses***;
    - **Ganirelix** and **Cetrorelix** are ***approved for*** use in ***controlled*** **ovarian stimulation**, **In Vitro Fertilization** (**IVF**); Inhibition of premature LH surges in women undergoing controlled ovarian stimulation.
    - **Degarelix** and **Abarelix** are ***approved for*** men with ***advanced*** **prostate cancer**.
- ***Common Side Effects***;
    - **Nausea** and **headache**.
    - ***Long term use*** (**Degarelix** and **Abarelix**); **injection-site reactions**, **hot flashes**, **weight gain** and ***increases*** in **liver enzymes**.

Posterior Pituitary

- **Posterior pituitary** (**Neurohypophysis**) is ***not*** **glandular** and ***not regulated*** by **releasing hormones** as is the **anterior pituitary**.
- The **posterior pituitary** *consists mainly* of **neuronal projections** (**axons**) of **magnocellular neurosecretory cells**.
- The **hormones** of the **posterior pituitary**, **Oxytocin** and **Vasopressin**, are ***synthesized*** in **cell bodies** of **magnocellular neurons** are ***located*** in **paraventricular nuclei** (**PVN**) and **supraoptic nuclei** (**SON**) of the **hypothalamus**.
- These **axons** ***store*** and ***release*** **neurohypophysial hormones Oxytocin** and **Vasopressin** into the **neurohypohyseal capillaries**, from there they ***get into*** the **systemic circulation**.
- The **hypothalamic–neurohypophyseal system** is ***composed of***;
    1) **Hypothalamus** (**paraventricular nucleus** and **supraoptic nucleus**).
    2) **Axonal projections**.
    3) **Posterior pituitary**.


Supraoptic nucleus (cells secrete oxytocin)
Neurosecretory cells
Paraventricular nucleus (cells secrete ADH)
Hypothalamus
Artery
Inflow of blood
Infundibulum
Axon terminals (release hormones to capillaries)
Anterior pituitary
Capillary bed
Posterior pituitary
Vein
Outflow of blood

- **Posterior pituitary** ***stores*** and ***releases*** **two hormones** ***secreted by*** the **hypothalamus**;
    - **Oxytocin**;
        - Is ***responsible*** for **uterine contractions**, ***before*** and ***after*** **delivery**.
        - Is also ***responsible*** for **milk ejection** ***during*** **breastfeeding**.
    - **Antidiuretic Hormone** (**ADH**) or **Vasopressin**;
        - ***Stimulates*** **water retention**; ***Antidiuretic effect***.
        - ***Raises*** **blood pressure** by ***contracting*** **arterioles**; ***Vasopressor effect*** → **Vasopressin**.

Antidiuretic Hormone (ADH)

- **Antidiuretic Hormone** (**ADH**) *or* **Vasopressin** *or* **Arginine Vasopressin** (**AVP**) *or* **Argipressin** are ***peptide*** **hormone** ***consisting*** of **9 amino acids** (nonapeptides), and is **structurally** ***related*** to **Oxytocin**.
- **Vasopressin** is ***released by*** the **posterior pituitary** in ***response to***;
  - ↑ **plasma tonicity** (hypertonicity) = ↑ **plasma osmolality** (hyperosmolality).
  - ↓ **blood pressure**.
- The ***half-life*** of ***circulating*** **Vasopressin** is *approximately* **15 minutes**.
- **Vasopressin** ***receptors*** (**AVP receptors**); all are G protein-coupled.

Type	Second Messenger	Actions
V1a (AVPR1A)	Gq activation (Phosphatidylinositol/calcium)	Vasoconstrictor action and platelet aggregation
V1b (AVPR1B) (V3)	Gq activation (Phosphatidylinositol/calcium)	Mediate release of ACTH
V2 (AVPR2)	Gs activation (Adenylate cyclase/cAMP)	Antidiuretic action

- ***Osmolality***;
  - **Plasma osmolality**; ***measures*** the **body's electrolyte-water *balance***; measured by osmometer.
  - **Urine osmolality**; ***measures*** the **urine electrolyte-water *balance***.

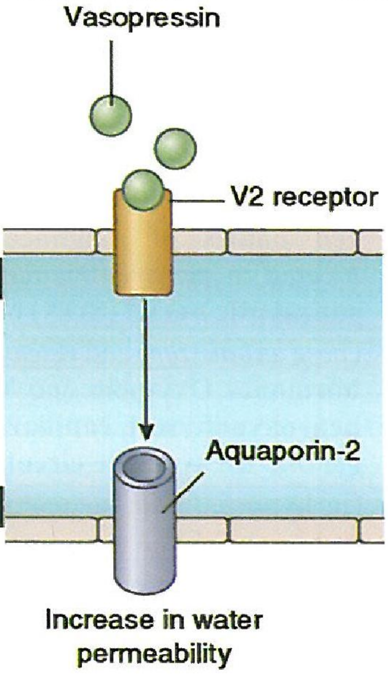
Normal Values

- ***Serum*** **ADH**; **1–5 pg/mL** (picogram/milliliter).
- ***Serum*** **Osmolality**; **275–295 mOsmol/kg** (milliosmoles per kilogram).
- ***Urine*** **Osmolality**;
  - **24-hour urine osmolality**; 500-800 mOsm/kg of water.
  - **Random urine osmolality**; 300-900 mOsm/kg of water.
  - ***After*** **12-14 hours** of **fluid intake *restriction***, the **urine osmolality should *exceed*** 850 mOsm/kg of water.

Function

Water Retention (Anti-diuretic) Effect

- **Vasopressin** ***binds*** to the **V2 receptor** → ***increase*** *formation* of **cAMP** which causes ***insertion*** **protein water channels** called **Aquaporin-2** in the **tubular cell** → ***increase permeability*** of ***these*** **cells** → ***increase*** **water reabsorption** by **passive diffusion (osmotic gradient)**.



Vasoconstriction Effect

- ***High*** **concentration** of **Vasopressin** can cause **vasoconstriction** by ***binding*** to **V1a receptors** (via activation of phospholipase C; PLC and consequent release of Ca^{2+} from the sarcoplasmic reticulum).

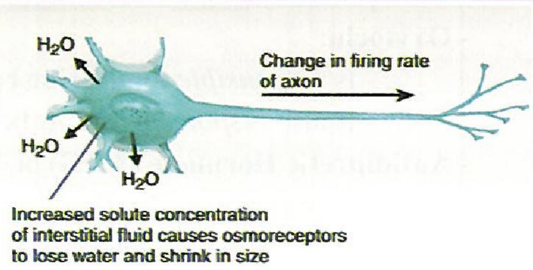
Other Effects

- **V1 (V1A)**; **Vasoconstriction**, ***stimulate*** **gluconeogenesis, platelet aggregation** and ***release*** of ***factor*** **VIII** and **von Willebrand factor**.
- **V3 (V1B)**; ***Stimulate*** **ACTH** ***secretion from*** **pituitary gland**.

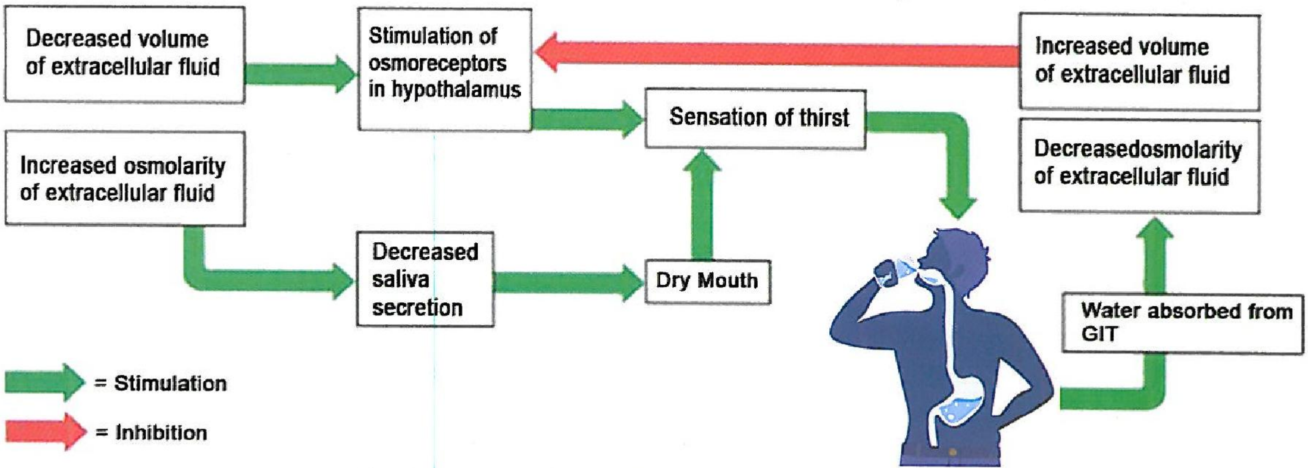
Regulation

Factors that increase ADH secretion

1) ***Increase*** **plasma osmolarity**;
- ↑ Plasma osmolarity (dehydration) → ↑ outflow of water from the osmoreceptors (detect change in osmotic pressure) in hypothalamus → Shrunken the cell → sent signal to the hypothalamus → which ↑ release & synthesis ADH.

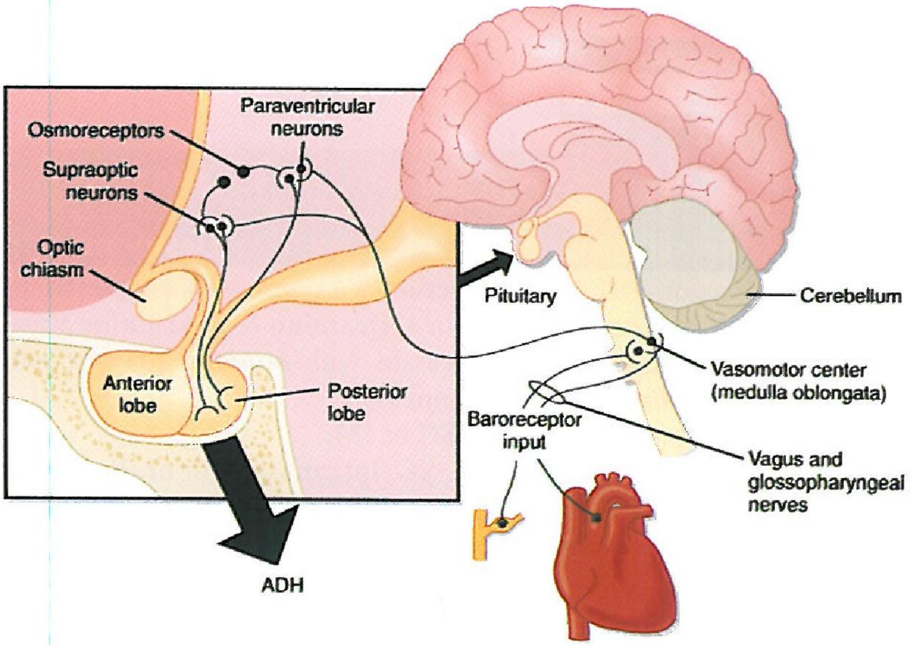

H_2O
H_2O
H_2O
Change in firing rate of axon
Increased solute concentration of interstitial fluid causes osmoreceptors to lose water and shrink in size

- **Thirst Mechanism**;
  - ↑ Osmolarity → Stimulation of osmoreceptors → ↑ sensation of thirst.
  - ↑ Osmolarity → ↓ saliva secretion → dray mouth → ↑ sensation of thirst.


Decreased volume of extracellular fluid
Increased osmolarity of extracellular fluid
Stimulation of osmoreceptors in hypothalamus
Sensation of thirst
Decreased saliva secretion
Dry Mouth
Increased volume of extracellular fluid
Decreasedosmolarity of extracellular fluid
Water absorbed from GIT
= Stimulation
= Inhibition

2) ***Decrease* blood volume**;
- Decreased blood volume → ↓ arterial blood pressure → baroreceptor detect decreased blood pressure → ↑ ADH secretion → Vasoconstriction.

Regulation


Osmoreceptors
Paraventricular neurons
Supraoptic neurons
Optic chiasm
Anterior lobe
Posterior lobe
ADH
Pituitary
Cerebellum
Vasomotor center (medulla oblongata)
Baroreceptor input
Vagus and glossopharyngeal nerves

3) **Angiotensin II**; **Angiotensin II *receptors*** *located* in a **region** of the **hypothalamus**; ↑ Angiotensin II → ↑ ADH secretion.

4) **Stress**; **Stress-*induced increase*** in **Vasopressin** and **ACTH**.

5) ***Some* drugs**; **Morphine** and **Nicotine**.

Factors that decrease ADH secretion

1) ***Decrease* plasma osmolarity**. 2) ***Increase* blood volume**.

3) ***Some* drugs**; **Cortisol**, **α-adrenergic agonists** and **Ethanol** (**Alcohol**).

Disturbance of Vasopressin Function

A) Vasopressin Hypersecretion (SIADH)

- **Syndrome** of **Inappropriate Antidiuretic Hormone Secretion** (**SIADH**); is **inappropriate *continued*** **secretion** or **action** of **Vasopressin** *lead to* ***impaired*** **water excretion** and ***increased*** **plasma volume** (**hyponatremia** and **hypo-osmolality**).
- **SIADH** is *most often **caused by*** **nervous system disorders**, **neoplasia**, **pulmonary diseases**, and **drug *induced*** (such as ***certain*** **Antidepressants**, **Carbamazepine**, **Oxytocin** and **Vincristine**).
- ***Pharmacotherapy***; **Vasopressin receptor antagonists** and **Demeclocycline** (**Tetracycline *antibiotic***)

B) Vasopressin Hyposecretion (Diabetes Insipidus)

- **Diabetes Insipidus** (**DI**) is a condition *characterized by* ***large*** **amounts** of ***dilute*** **urine** (**Diabetes**), **tasteless** (**insipidus**) and ***increased*** **thirst**.
- There are **4 types** of **DI**, with a ***different*** **causes**;

Neurogenic (Central)	- ***More*** **commonly**. - *Due to* a ***lack*** of **Vasopressin** ***production*** in the **brain**. - ***Causes***; **Idiopathic**, **tumors** of the **brain** or **pituitary**, **cranial surgery** and **head trauma**.
Nephrogenic	- *Due to* the ***inability*** of the **kidney** to **respond** ***normally*** to **Vasopressin**.
Gestational	- ***Only*** occurs ***during*** **pregnancy**. - ***During*** **pregnancy**, **women** ***produce*** **Vasopressinase** in the **placenta**, which ***breaks down*** **Vasopressin**.
Dipsogenic	- ***Excessive*** **fluids intake**, *due to* a ***defect*** or ***damage*** to the **thirst mechanism**.

- ***Only*** **Central** and **Gestational Diabetes Insipidus** are *respond to* **Vasopressin** (Vasostrict®) and **Vasopressin** ***Analogue***; **Desmopressin** (Minirin®).

	Diabetes Insipidus	**Diabetes Mellitus**
Polyuria and Polydipsia	Sever	Less sever
Glucosuria	Absent	Present
Urine specific gravity	Very low	High
Urine color	Colorless	Yellow color
Urine pH	Neutral	Acidic

Vasopressin and its Analogues

Vasopressin (Vasostrict®)

Desmopressin (DDAVP®) (Minirin®)

- **Vasopressin** [vas-oh-PRESS-in] **injection** is a ***synthetic*** **Vasopressin hormone** for **IV**, **SC** or **IM** ***use***.
- **Desmopressin** [des-moe-PRESS-in] or **1-Deamino-8-D-Arginine VasoPressin** (**DDAVP®**) is a ***long-acting*** **synthetic analog** of **Vasopressin** with ***minimal*** **pressor activity** and an **antidiuretic-*to*-pressor** ***ratio*** **4000** ***times*** that of **Vasopressin**.
- ***Administration***; - **Vasopressin**; **IV**, **SC** or **IM**.
  - **Desmopressin**; **IV**, **SC**, **intranasally** or **orally** (***Regular*** or ***melt*** **tablets**).
    - **Nasal administration** of **Desmopressin** may be ***less effective*** when **nasal congestion** is *present*.

Therapeutic Uses

- **Desmopressin** (**Minirin®**);
  - **Diabetes Insipidus**.
  - **Hemophilia A** and **von Willebrand disease** (**Type I**).
  - **Bedwetting** (**Nocturnal Enuresis**) and **Nighttime Urination**.
- **Vasopressin** (**Vasostrict®**);
  - **IM/SC**; **Diabetes Insipidus**, **Abdominal Distention** and **Abdominal Roentgenography**.
  - **IV *infusion***; **Esophageal variceal bleeding** and **colonic diverticular bleeding**.
  - **IV *bolus***; in **pulseless arrest** (In ***replacement*** of **Epinephrine** in the **Advanced Cardiovascular Life Support**; **ACLS *resuscitation* protocol**).

- ***Side effects***; - **Headache**, **nausea**, **abdominal cramps** and **agitation**.
  - ***Overdosage*** can result in **hyponatremia** and **seizures**.

Vasopressin Receptor Antagonists

Conivaptan (Vaprisol®)

Tolvaptan (Samsca®)

- **Conivaptan** [koe-NYE-vap-tan] and **Tolvaptan** [tol-VAP-tan] are ***approved*** by the **FDA** for ***treatment*** for **hyponatremia** ***associated with*** **CHF**, **cirrhosis** and **SIADH**.
- ***Other*** **Vasopressin Receptor Antagonists** ***under development***; **Mozavaptan** (approved in Japan), **Relcovaptan**, **Nelivaptan**, **Lixivaptan** and **Satavaptan**.

Oxytocin

- **Oxytocin** is a **9-amino-acid peptide** with an **intrapeptide disulfide** ***cross-link*** *like* **Vasopressin**, ***but*** **amino acid sequence** ***differs from*** that of **Vasopressin** at *positions* **3** and **8**.
- **Oxytocin** is *produced by* **hypothalamus** and *released by* **posterior pituitary** in *response to* **stretching** of the **cervix** and **uterus** ***during*** **labor** and with ***stimulation*** of the **nipples** *from* **breastfeeding**.
- The word **Oxytocin** was *derived from* **Greek** "**oxys**" and '**tokos**" ***meaning*** "**quick birth**".
- **Oxytocin** is ***rapidly*** **eliminated** by the **kidneys** and **liver**, with a ***circulating*** **half-life** of **5 minutes**.
- **Oxytocin** acts through **G protein–coupled receptors** (Gq activation; Phosphatidylinositol/calcium) to ***contract*** **uterine smooth muscle**.

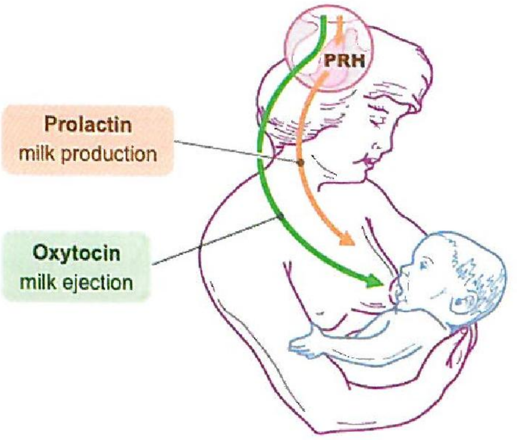
Function

During Labour (Uterine Contraction)

- ***In small*** **doses**; ***increases*** both the **frequency** and the **force** of **uterine contractions**.
- *At* ***higher*** **doses**; *produces* ***sustained*** **contraction**.
- **Oxytocin** also ***stimulates*** the ***release*** of **Prostaglandins** and **Leukotrienes** that ***augment*** **uterine contraction**.

During Lactation/Suckling (Milk Ejection)

- **Oxytocin** also *causes* **contraction** of **myoepithelial cells** ***surrounding*** **mammary alveoli**, which *leads to* **milk ejection**.
- **Milk Ejection Reflex**; ***Suckling*** by the **infant** at the **nipple** is ***relayed by*** **spinal nerves** to the **hypothalamus**, *causing*; **Oxytocin** and **Prolactin** ***release*** from the ***posterior*** **pituitary**.
- ***Without*** **Oxytocin**-***induced*** **contraction**, ***normal*** **lactation** ***cannot*** **occur**.



During Sexual Intercourse (Orgasm)

- **Oxytocin** (**Love Hormone**) is **now** ***believed*** to be **involved** in a ***wide variety*** of **physiological** and **pathological functions** *such as* **sexual activity**, **orgasm**, and **ejaculation**, **maternal behavior**, **social bonding**, **stress** and ***probably many more***.

Other

- At ***high*** **concentrations**, **Oxytocin** has ***weak*** **antidiuretic** and **pressor** ***activity due to activation*** of **Vasopressin receptors**.

Regulation

- **Oxytocin** ***Stimulus*** **Factors**;
  - ***Dilatation*** of the **cervix**; ***during*** **labour**.
  - ***Massage*** of the **nipple**; by **suckling**.
  - **Genital** ***stimulation*** (male and female); ***during*** **sexual intercourse**.
  - **Positive feedback** (+); ***increase*** in **hormone** ***stimulate further*** **secretion**.
  - **Estrogen**; ***increases*** **responsiveness** to **Oxytocin** by ***increasing*** **expression** of **Oxytocin receptors**.

Oxytocin and its Analogues

Oxytocin (Pitocin®) (Syntocinon®)

- **Oxytocin** [oks-i-TOE-sin] **injection** is a ***synthetic*** **Oxytocin hormone** for **IV** ***infusion*** or **IM** ***use***.
- *Uses*;
    - **Labor Induction**.
    - **Postpartum Hemorrhage**.
    - ***Adjunctive therapy*** in the **management** of ***incomplete*** or ***inevitable*** **abortion**.
- **Oxytocin nasal spray** ***uses*** (Off-label); ***Promote*** **Lactation**, **Autism**, ***Delayed*** **Orgasm** and **Intensifying Sexual Arousal**.
- **WARNINIG**; ***Excessive*** **stimulation** of **uterine contractions** ***before*** **delivery** can *cause* ***fetal*** **distress**, **placental** ***abruption***, or **uterine** ***rupture***; **Oxytocin injection** in **Labor Induction** is ***administered*** **ONLY** by the **IV** ***infusion*** and with ***adequate*** **medical supervision** in a **hospital**.
- *Toxicity*;
    - ***High*** **concentrations** of **Oxytocin** can ***activate*** of **Vasopressin receptors** can cause ***excessive*** **fluid retention** ***leading*** to **hyponatremia, heart failure, seizures** and **death**.
    - **Bolus** ***injections*** of **Oxytocin** can cause **hypotension**.
- *Contraindications*; **Fetal distress, fetal malpresentation, placental abruption**, and ***other predispositions*** for **uterine rupture**, *including* ***previous*** **extensive uterine surgery**.

Carbetocin (Duratocin®)

Demoxytocin (Sandopart®)

- **Carbetocin** and **Demoxytocin** are **Oxytocin** ***analogues*** with ***longer*** **half-life**.
- They are ***not*** **approved** by **US FDA**, but ***approved*** in ***some*** **countries** for *used* to ***induce*** **labor**, ***promote*** **lactation**, and **postpartum hemorrhage**.

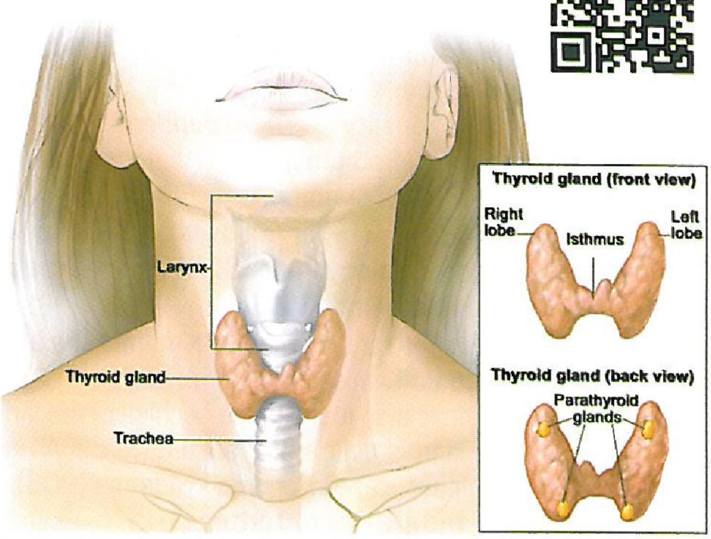
Oxytocin Antagonists

Atosiban (Tractocile®)

- **Atosiban** is an **Oxytocin** ***receptor antagonist*** that has been ***approved outside*** the **United States** as a **treatment (tocolysis)** for **preterm labor** (**tocolytic agent**).
- **Atosiban** is ***useful*** in ***improving*** the **pregnancy outcome** of **In Vitro Fertilization-Embryo Transfer** (**IVF-ET**) in **patients** with ***Repeated*** **Implantation Failure (RIF)**.
- **Barusiban** (Ferring) **Epelsiban** and **Retosiban** (GlaxoSmithKline) are **Oxytocin Receptor Antagonists** ***under development***.

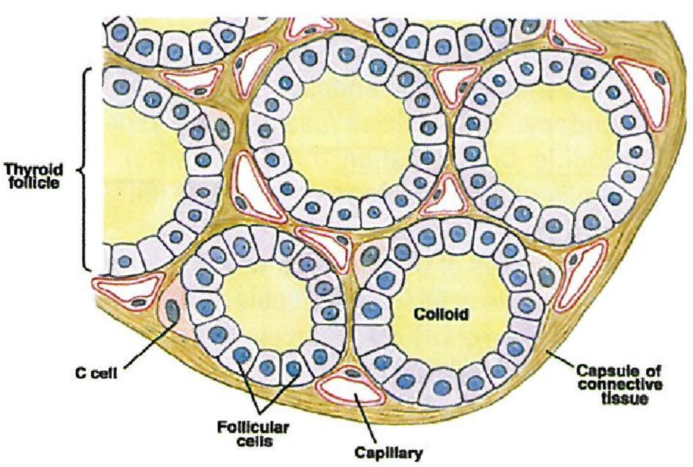
Thyroid Hormones

- The **thyroid gland**, is an **endocrine gland** ***found*** at the ***front of*** the **neck**, ***below*** the **Adam's apple**.
- It is a **butterfly-shaped organ** and is ***composed of*** **two lobes**; **right** and **left**.
- It is ***composed of*** **spherical follicles** that ***selectively*** **absorb Iodine** (as **Iodide ions**, I^-) ***from*** the **blood** for ***production*** of **thyroid hormones**, but also for ***storage*** of **Iodine** in **Thyroglobulin**.
- **Thyroid follicles**, each ***surrounds*** a cavity ***full of*** **colloid material**.
- **Colloid** is ***rich in*** a **Thyroglobulin (Tg)**
- **Colloid** ***act as*** **reservoir materials** for **thyroid hormones**.

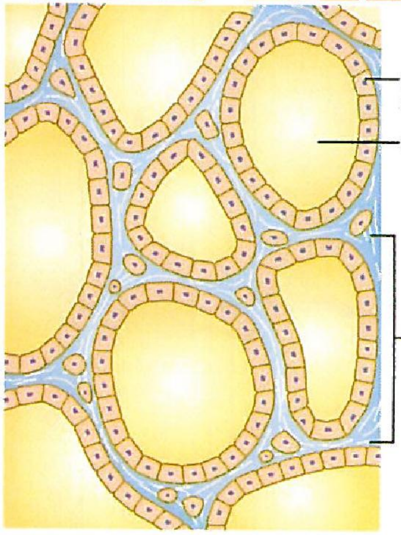

Larynx
Thyroid gland
Trachea
Thyroid gland (front view)
Right lobe
Isthmus
Left lobe
Thyroid gland (back view)
Parathyroid glands

- **Thyroid hormones**; **Thyroxin** or **Tetraiodothyronine** (T_4) and **Triiodothyronine** (T_3) are *secreted* by **thyroid follicles** to *normalize* **growth** and **development**, **body temperature** and **energy** *levels*.
- **Parafollicular cells** (**C- cells**) *secrete* **Calcitonin** (**Thyrocalcitonin**); the *second* **type** of **thyroid hormone**, is **important** *in* the *regulation* of **calcium metabolism**; acts to *reduce* **blood Calcium** (Ca^{2+}), *opposing* the effects of **Parathyroid hormone** (**PTH**).
- T_3 is **3-4 times *more* potent *than*** T_4.
- **Thyroid gland** is *not* **essential** for life, *inadequate* **secretion** of **thyroid hormone** *called* **hypothyroidism** and an *excess* **secretion** of **thyroid hormones** *called* **hyperthyroidism**.

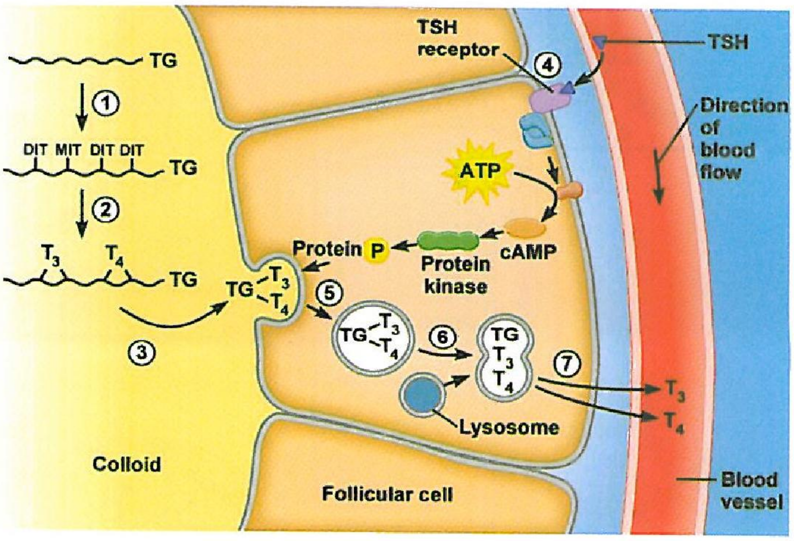
Section of thyroid gland


Thyroid follicle
Colloid
C cell
Follicular cells
Capillary
Capsule of connective tissue

- **Biosynthesis** of **Thyroid Hormones**;


Follicular cell
Colloid
Follicle

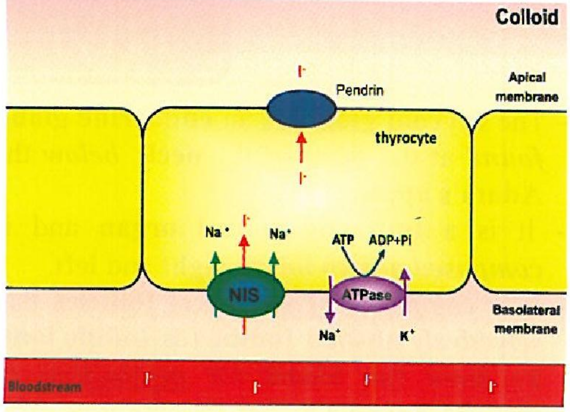
Thyroid follicles


TG
①
DIT MIT DIT DIT
TG
②
T3 T4
TG
③
TG-T3 T4
TSH receptor
④
TSH
Direction of blood flow
ATP
Protein P
Protein kinase
cAMP
⑤
TG-T3 T4
⑥
TG T3 T4
⑦
T3
T4
Lysosome
Colloid
Follicular cell
Blood vessel

Synthesis and secretion of thyroid hormones

- **Tyrosine** *residues* of **Thyroglobulin** (**TG**) are **iodinated**. **One iodide** *added* to **tyrosine** *forms* **Mono-IodoTyrosine** (**MIT**), **two iodide** *added* *forms* **Di-IodoTyrosine** (**DIT**).
  - **Two DIT** *form* **T4** (**Tetraiodothyronine**).
  - **One MIT** and **one DIT** *forms* **T3** (**Tri-iodothyronine**).

1) **Iodide Trapping**;


Colloid
Pendrin
Apical membrane
thyrocyte
I⁻
I⁻
I⁻
Na⁺
Na⁺
ATP
ADP+Pi
NIS
ATPase
Basolateral membrane
Na⁺
K⁺
Bloodstream
I⁻
I⁻
I⁻
I⁻

- **Iodide** ***trapping*** through the **follicular cell** by **Sodium/Iodide Symporter** (**NIS**); ***first*** **transport**.
- **Na^+/I^- Symporter** ***transports*** **2 Sodium** ***ions across*** the **basement membrane** of the **follicular cells** ***along with*** **1 Iodide** ion.
- **NIS functionality** is ***dependent*** on the ***electrochemical*** **Sodium** ***gradient*** that is ***maintained by*** the **Na^+/K^+ATPase pump**.
- **NIS** can be ***inhibited*** by **large** ***doses*** of **Iodide** as well as **anions** (e.g., **Thiocyanate** (**SCN^-**), **Pertechnetate** (**TcO_4^-**) and **Perchlorate** (**ClO_4^-**).
- ***Second*** **transport**; at the **apical cell membrane** a ***second*** **I^- transport enzyme** *called* **Pendrin controls** the ***flow*** of **Iodide** ***across*** the **membrane**;
  - Pendrin is also found in the cochlea of the inner ear.
  - If Pendrin is deficient or absent (SLC26A4 gene mutation), a hereditary syndrome of goiter and deafness, called Pendred syndrome (PDS).

2) **Oxidation** of **Iodide** (I^-) ***to*** **Iodine** (I_2);

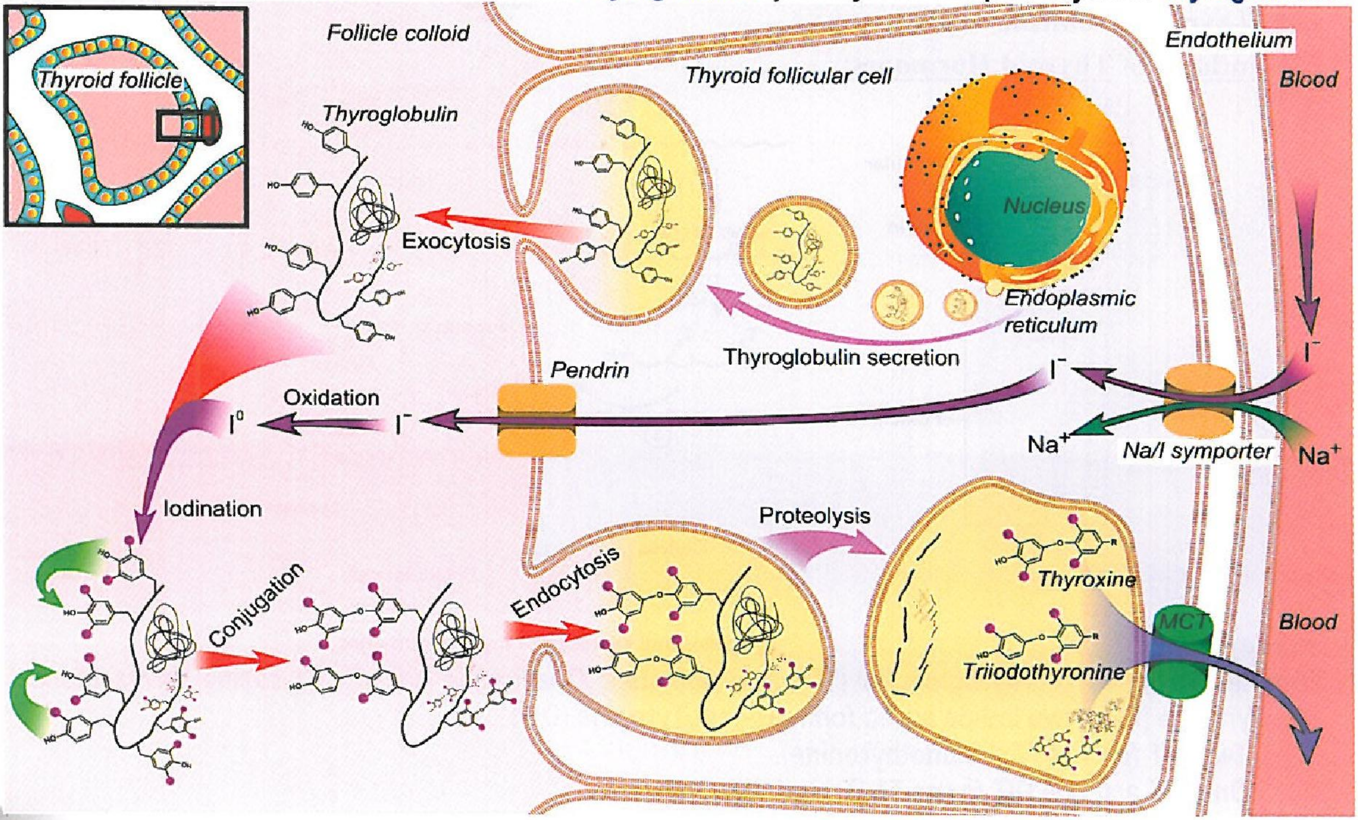
- In the **colloid**, **2 Iodide** (I^-) is **oxidized** ***to*** **Iodine** (I_2) by **Thyroid Peroxidase Oxidizes** (**TPO**) ***enzyme***. **TPO** is ***stimulated by*** **TSH**.

3) **Iodination** of **Tyrosine**;

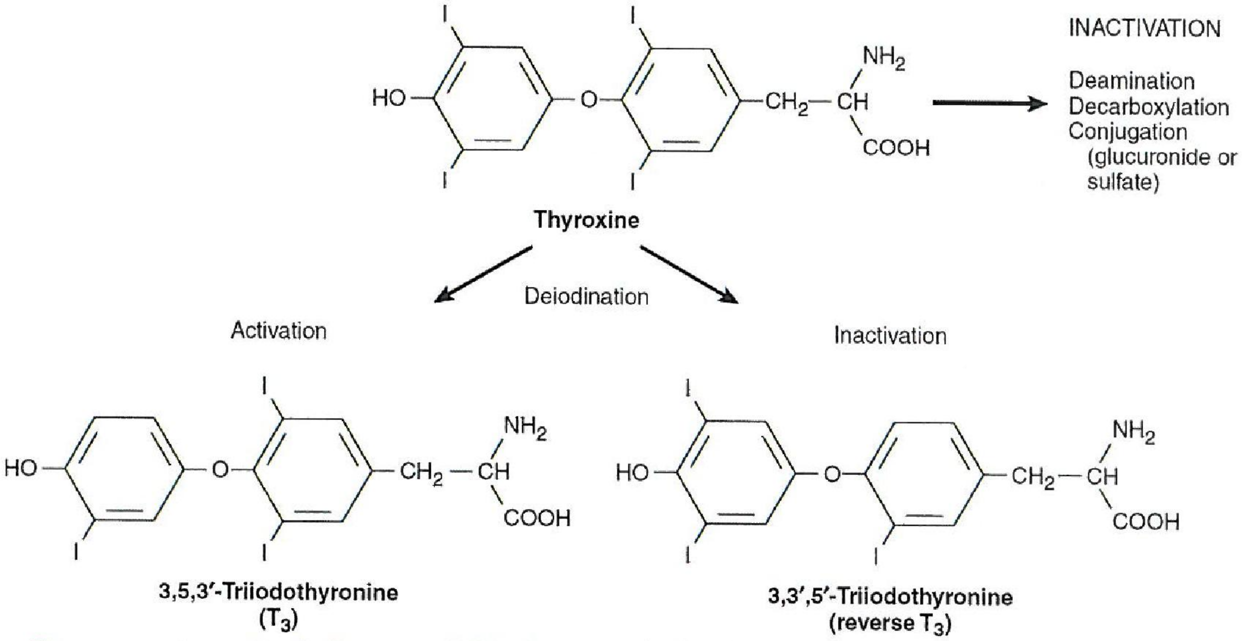
- ***Each*** **Thyroglobulin** molecule ***contains*** *approximately* **100-120 Tyrosine residues**, but only a ***small number*** (**20**) of these are ***subject to*** **iodination** by **Thyroid peroxidase** in the **follicular colloid**.
- **TSH** ***stimulates*** the **endocytosis** of the **colloid**.
- **Endocytosed vesicles** ***fuse*** with the **Lysosomes** of the **follicular cell**.
- **Iodide Organification** (*organic binding*); ***iodinates*** **Tyrosine residues** ***within*** the **Thyroglobulin** ***molecule*** to ***form*** **Monoiodotyrosine** (**MIT**) and **Diiodotyrosine** (**DIT**).

4) **Coupling**;

- **2 molecules** of **DIT combine** ***within*** the **Thyroglobulin molecule** to ***form*** **Thyroxine** (T_4).
- **1 molecule** of **MIT** & **1 molecule** of **DIT** ***combine*** to ***form*** **T_3**.
- **1 molecule** of **DIT** & **1 molecule** of **MIT** ***combine*** to ***form*** **reverse T_3** (**rT_3**); Coupling in the opposite order and is **biologically** inactive.
- **T_4**, **T_3**, **MIT**, and **DIT** are ***released*** from **Thyroglobulin** by **exocytosis** and **proteolysis** of **Thyroglobulin**.


Thyroid follicle
Follicle colloid
Thyroid follicular cell
Endothelium
Blood
Thyroglobulin
Nucleus
Exocytosis
Endoplasmic reticulum
Thyroglobulin secretion
Pendrin
I⁻
I⁻
Oxidation
I⁰
I⁻
Na⁺
Na/I symporter
Na⁺
Iodination
Proteolysis
Conjugation
Endocytosis
Thyroxine
Triiodothyronine
MCT
Blood

- **Notes**;
  - **Plasma Protein Binding**; T_4 and T_3 in **plasma** are *reversibly* **bound** to **protein**, primarily **Thyroxine-binding Globulin (TBG)**; *Only* about **0.04%** of total T_4 and **0.4%** of T_3 *exist* in the *free* **form** (as FT_4 and FT_3).
  - The **ratio** of T_4 to T_3 *within* **Thyroglobulin** is *approximately* **5:1**, so that *most* of the **hormone** *released* is **Thyroxine**.
  - **Peripheral metabolism** (**Deiodination**); T_4 is *converted to* T_3 *as required* in the **peripheral tissues** by **Iodothyronine Deiodinase** *enzyme* (**80%** of T_3 *circulating* in the **blood** is *derived from* **peripheral metabolism** of **Thyroxine**).



INACTIVATION
Deamination
Decarboxylation
Conjugation (glucuronide or sulfate)
Thyroxine
Deiodination
Activation
Inactivation
3,5,3′-Triiodothyronine (T3)
3,3′,5′-Triiodothyronine (reverse T3)

  - **Drugs** *such as* **Amiodarone**, **β-blockers** and **Corticosteroids**, *as well as* **severe illness** or **starvation**; *inhibit* the **Deiodinase enzyme** *necessary for* the *conversion* of T_4 to T_3.
  - **Endocrine Regulation**;
    - **Thyroid-stimulating Hormone (TSH)** *stimulates* *synthesis* and *release* of T_4 and T_3.
    - *More* **active** T_4 to T_3, acts in a **negative feedback** *inhibition* in the **pituitary** to *block* the **action** of **TSH** and in the **hypothalamus** to *inhibit* the *synthesis* and *secretion* of **Thyrotropin Releasing Hormone (TRH)**.
  - **Autoregulation** *of* **Thyroid Gland**;
    - The **thyroid gland** also *regulates* its **uptake** of **Iodide** and **thyroid hormone** *synthesis* (*independent* to **TSH**) in *response to* the **level** of **Iodine** in the **blood**.
    - **Hypothyroidism** can be *caused by* **Iodine** *Deficiency* or **Iodine** *Excess*!!
    - *Excess* of **Iodine** *inhibit* **Iodide Organification** (**Thyroglobulin Iodination**); known as the **Wolff-Chaikoff block**;
      - In **1948**, **Wolff** and **Chaikoff** *reported* that **injection** of **Iodine** in **rats** *almost* **completely** *inhibited* **organification** in the **thyroid gland**.
      - The *acute* **Wolff-Chaikoff effect** *lasts* for *few* **weeks** and *then*, the **thyroid gland** escapes the **Wolff-Chaikoff effect** (**escape phenomenon**) *because* **autoregulatory mechanisms** *inhibit* **thyroid iodide transport** (**down regulation** of the **Sodium Iodine Symporter**; **NIS**) and the *intrathyroidal* **iodine concentration** consequently *falls below* the *level required for* **inhibition** of **organification** and the *normal* **synthesis** of T_4 and T_3 *returns*.
      - The **Wolff–Chaikoff effect** also *explains* the **hypothyroidism** produced in *some* **patients** by *several* **Iodine-containing Drugs**, including **Amiodarone**.
      - In **certain disease** states (e.g., **Hashimoto's thyroiditis**), the **gland** *cannot* escape *from* **Wolff–Chaikoff effect**, *causing* **hypothyroidism**.
      - **Hyperthyroidism** can *result from* the *loss* of the **Wolff-Chaikoff block** in *susceptible* **individuals** (e.g., **multinodular goiter**).

Thyroid Hormones

Levothyroxine or **L-thyroxine** (Euthyrox®)	**Liothyronine** (Cytomel®)

- **Thyroxine** (T_4) and **Triiodothyronine** (T_3) as well as *reverse* **Triiodothyronine** (rT_3) are ***natural* thyroid hormones** and they are *levo* (*l*) **isomers**; **synthetic** *dextro* (*d*) **isomer** of **Thyroxine**, **Dextrothyroxine**, has *approximately* **4%** of the **biologic activity** of the **Levothyroxine**.
- **Levothyroxine** [LEE-voe-thye-ROX-een] or **L-thyroxine**, is a *synthetic* **form** of **Thyroxine** (T_4).
- **Liothyronine** [LYE-oh-THYE-roe-neen] is a *synthetic* **form** of **Triiodothyronine** (T_3).
- **Liotrix** [LYE-oh-triks] (**Thyrolar®**) is a **4:1** *mixture* of T_4 and T_3 *made synthetically*.
- **Tiratricol** (*also known as* **TRIAC** or **Triiodothyroacetic acid**) is a **thyroid hormone** ***analogue*, used** as a **dietary supplement** for **thyroid problems** it is also **used** for *increasing* **metabolic rate** for **weight loss** and *reducing* **cellulite**; US FDA warnings to use of dietary supplements containing **Tiratricol**.

Normal Values

- **Typical Adult Values** *for* ***Common* Thyroid Function Tests**; *Medscape*

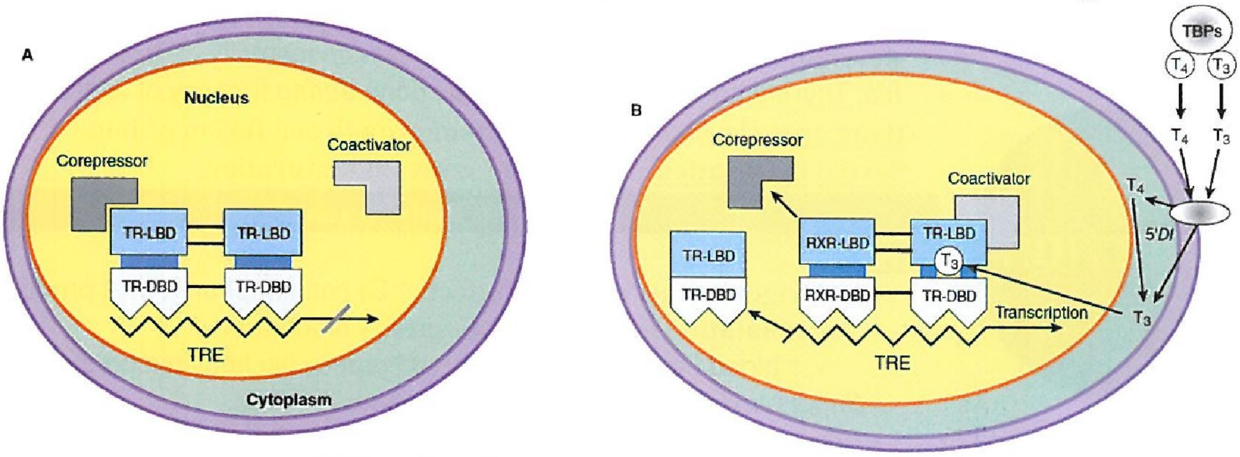
Test	Normal Value	Hypothyroidism	Hyperthyroidism
Total T_4	5.4–11.5 mcg/dL	Low	High
Total T_3	80-220 ng/dL	Normal or low	High
Free T_4 (FT_4)	0.7-1.8 ng/dL	Low	High
Free T_3 (FT_3)	260-480 pg/dL	Low	High
TSH	0.4-4.2 mIU/L	High	Low

Each laboratory has its own reference range depending on method

Pharmaco Kinetics

- ***Absorption***; *Both* T_4 and T_3 are **absorbed** *after* **oral administration.**
  - **Oral bioavailability**; T_4; **70-80%.** T_3; *completely* **absorbed (95%)**.
  - **Food**, **Calcium** *preparations* and **Aluminum-*containing* antacids** can *decrease* the **absorption** of T_4 (**Fatty meal** and **coffee** *lowers* its **absorption**); **Thyroid hormones** ***must be* taken** in the **fasting state** (30-60 minutes before breakfast).
  - **Absorption** is *not* to be **affected** by ***mild* hypothyroidism** but may be *impaired* in *severe* **hypothyroidism**; *switching from* **oral** to **parenteral therapy** (IV is preferred).
- ***Distribution***;
  - *More than* **99%** of *circulating* **thyroid hormones** are *bound* to **plasma proteins**; *primary to* **Thyroxine-binding Globulin** (**TBG**) and *some to* **Thyroxine-binding Prealbumin** (**TBPA**); T_4 has *higher affinity* than T_3.
  - **Unbound** (**Free**) T_4 and T_3 are the *active* **forms** and *gain* entry *into* the **cell** by an **ATP** *dependent* **process.**
  - **Aspirin** (**Salicylates**), **Phenytoin**, **Carbamazepine** & **Furosemide** are *displace* T_4 and T_3 *from* **serum binding proteins.**
  - **Pregnancy**, **Estrogens** & **Tamoxifen** → ↑ **TBG concentration,** *while* **Androgens**, **Corticosteroids** & **Niacin** → ↓ **TBG.**
- ***Metabolism***;
  1) **Sequential Deiodination** (major route of metabolism); *About* **80%** of *circulating* T_3 *obtained from* T_4 **deiodination** *mainly* in the **liver** & **kidneys**; **Amiodarone**, **Propranolol** & **Corticosteroids** → **inhibits** *conversion* of T_4 to T_3.
  2) **Conjugation *with* Glucuronides** and **Sulfates**; *excreted* in **feces.**
  3) **Deamination** and **Decarboxylation** *excreted* in **urine.**
  - **Drugs** that *induce* **hepatic microsomal enzymes** (e.g., **Rifampin**, **Phenobarbital**, **Phenytoin**, **HIV protease inhibitors**) *increase* the **metabolism** of *both* T_4 and T_3.
- ***Elimination***; **Urine** (major) and **feces** (20%).
  - *Half-life*: - T_3; 1-2 days.
    - T_4; 9-10 days (hypothyroid); 3-4 days (hyperthyroid); 6-7 days (euthyroid).

	Thyroxin (T_4)	Triiodothyronine (T_3)
Origin	Thyroid (100%)	- Thyroid (20%) - Deiodination of T_4 (80%)
Potency	1	4
Oral bioavailability	70-80%	95%
Half life	7 days	1 day
Protein binding form	99.96%	99.6%
Free form	0.04%	0.4%
Total serum level	5–11 mcg/dL	0.1–0.2 mcg/dL



Mechanism OF Action

A: **Inactive phase**; the ***unliganded*** **T_3 receptor dimer** ***bound*** to the **thyroid hormone response element (TRE)** ***along with*** **corepressors** ***acts as*** a ***suppressor*** of **gene transcription**.

B: **Active phase**;

- **T_3** and **T_4** **circulate** ***bound to*** **thyroid-binding proteins (TBPs)**.
- The ***free*** **hormones** are **transported** ***into*** the **cell** by a **specific transport system**.
- ***Within*** the **cytoplasm**, **T_4** is ***converted to*** **T_3** by **5′-deiodinase (5′DI)**.
- **T_3** then ***moves*** into the **nucleus**.
- **T_3** ***binds*** to the **ligand-binding domain** of the **thyroid receptor (TR) monomer**.
- This ***promotes*** **disruption** of the **TR homodimer** and **heterodimerization** with **retinoid X receptor (RXR)** on the **TRE**, ***displacement*** of **corepressors**, and ***binding*** of **coactivators**.
- The **TR-coactivator complex** ***activates*** **gene transcription**, which leads to ***alteration*** in **protein synthesis** and **cellular phenotype**.

Function

- **Thyroid hormones** are ***responsible for*** **optimal growth**, **development**, **function**, and **maintenance** of ***all*** **body tissues**.
- **Thyroid hormones** is ***critical for*** the **development** and **functioning** of **nervous**, **skeletal** and **reproductive tissues**.

Effect on Cell Metabolism

- **Mitochondria**; ↑ **size** & **number** of **mitochondria** → ↑ **ATP** ***formation***.
- **Cell Membrane**; ↑ ***activity*** of **Na^+/K^+ ATPase** ***enzyme*** → ↑ **Na^+/K^+ transport** → ***energy*** **consumption** and **heat** ***production***.

Effect on Body Metabolism

Thyroid hormones ***Stimulate*** **Basal Metabolic Rate (BMR)**

[↑ ***levels*** of **Thyroid** → ***slight*** ↑ **body temperature** and ↓ **heat tolerance**]

- **Carbohydrate**; ***Stimulate all*** **carbohydrate metabolism** (insulin secretion, glucose uptake by the cell, glycolysis and gluconeogenesis).
- **Protein**; ***Stimulate both*** **protein** ***synthesis*** and ***degradation***.
- **Fat** (**lipolytic**); ***increase*** **fat breakdown** (**lipolysis**) & ***decrease*** **fat store**.

Function

- **Plasma Lipids**;
  - *Increase* **free fatty acids** *levels* in the **plasma** and *accelerates* **oxidation** of **free fatty acids** by the **cells**.
  - *Decrease* **cholesterol**, **triglyceride** and **phospholipids** *levels* of in the **plasma**; *increased* **risk** of **coronary artery disease** in **hypothyroid patient**.
- **Vitamins**; *Increased* **need** *for* **vitamins**; **vitamins** (co-enzymes) are **essential** for *many* **metabolic process**.

Effect on Growth

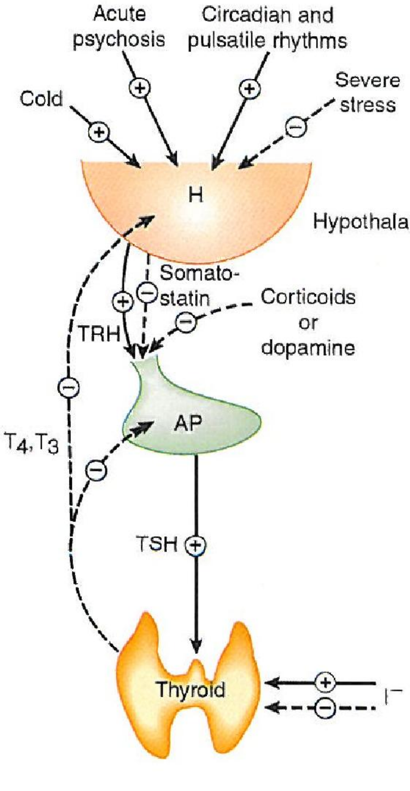
- **Mental development**; *Importance* in **fetal** for *normal* **mental development**; **fetal** *without* **thyroid** will *remain* **mentally deficient** *throughout* **life**; Thyroid hormones test *should* be done *during* **first day** of **fetal life**).
- **Bone growth**; *Important* for *normal* **growth** and **fusion** of **bone**.
- **Sexual maturation**; *Important* for **sexual maturation**.

Effect on Body System

- **CVS**;
  - **Calorigenic** (**thermogenic**) **effect**; ↑ O_2 **consumption** & **heat production**
  - **Vasodilatation** in *most* **body tissues**; ↑ **blood flow**;
    - ↑ **blood flow** to the **skin** to *try* and *reduce* the **body temperature**.
  - *Supersensitivity* of **sympathetic nervous system**.
  - *Increase* **cardiac output** and **heart rate** (**tachycardia**).
  - *Increase* **respiration**.
  - **Diuretic effect**.
- **CNS**;
  - **Mental development**.
  - *Excitatory* **effect** on **CNS**.
    - *Too little* **thyroid hormone** can *cause* **mentally sluggish**.
    - *Too much* **thyroid hormone** can *cause* **anxiety** and **nervousness**.
- **GIT**;
  - *Increase* **GI Motility** (*increase* **appetite** and **food intake**);
    - **Hyperthyroidism** can cause **diarrhea**
    - **Hypothyroidism** can cause **constipation**.

Regulation

- **Acute psychosis** or *prolonged* **exposure** to **cold** may *activate* **hypothalamic-pituitary-thyroid axis**.
- **Hypothalamic thyroid-releasing hormone** (**TRH**) *stimulates* **pituitary thyroid-stimulating hormone** (**TSH**) *release*, *while* **somatostatin** and **dopamine** *inhibit* **it**.
- **TSH** *stimulates* **T4** and **T3** *synthesis* and *release* **from** the **thyroid**, and they in *turn* *inhibit* *both* **TRH** and **TSH** *synthesis* and *release*.
- *Small* **amounts** of **iodide** are *necessary for* **hormone** *production*, *but large* **amounts** *inhibit* **T3** and **T4** *production* and *release*.



Notes

- The **recommended daily** ***adult*** **Iodide** (I^-) ***intake*** is **150 mcg (200 mcg** ***during*** **pregnancy** and **lactation** and ***up to*** **250 mcg** for **children**).
- **Pregnant women** and **nursing mothers** can ***safely*** **take Levothyroxine, hypothyroidism** have an ***increased*** **risk** of **miscarriage**; ***need monitoring every*** **6-8 Week**.

- ***Therapeutic Uses***; ***Treatment of*** **Hypothyroidism** (*see next*).
  - **Levothyroxine** (T_4) is ***preferred over*** **Liothyronine** (T_3) or T_3/T_4 ***combination***; it is ***better*** **tolerated** and has a ***longer*** **half-life** (**Levothyroxine** is the ***drug*** of ***choice in*** **Hypothyroidism**).
  - **Levothyroxine** is ***dosed*** **once daily**, and **steady state** is ***achieved*** in **6-8 weeks** (Monitoring of the patient's condition and adjustment of the dosage are necessary).
- **FDA Warning**; **Thyroid hormones**, *either* ***alone*** or ***with*** *other* **therapeutic agents**, ***should*** **NOT** be used for the ***treatment of*** **obesity** or for **weight loss**.
- ***Toxicity*** (***symptoms*** of **hyperthyroidism**); *such as* **Nervousness, palpitations** and **tachycardia, heat intolerance**, and ***unexplained*** **weight loss**.
- **Drug Effects** and **Thyroid Function**;

A) Change in Thyroid Hormone Synthesis;	
Inhibition of TRH or TSH secretion without induction of hypothyroidism or hyperthyroidism	Bexarotene, Dopamine, Bromocriptine, Cabergoline, Levodopa, Corticosteroids, Somatostatin, Octreotide, Metformin, Interleukin-6, Heroin.
Inhibition of thyroid hormone synthesis or release with the induction of hypothyroidism (or occasionally hyperthyroidism)	Iodides (including Amiodarone), Lithium, Aminoglutethimide, Thioamides, Ethionamide, Tyrosine kinase inhibitors (e.g., Sunitinib, Sorafenib, Imatinib), HIV protease inhibitors.
B) Alteration of Thyroid Hormone Transport and Serum Total T_3 and T_4 Levels, but Usually No Modification of FT_4 or TSH;	
Increased Thyroxine-binding Globulin (TBG)	Estrogens, Tamoxifen, Raloxifene, Heroin, Methadone, Mitotane, 5-fluorouracil, Perphenazine.
Decreased Thyroxine-binding Globulin (TBG)	Androgens, Anabolic steroids, Glucocorticoids, Danazol, l-asparaginase, Nicotinic acid (Niacin; Vitamin B3)
Displacement of T_3 and T_4 from TBG with transient hyperthyroxinemia	Salicylates, Fenclofenac, Mefenamic acid, IV furosemide, Heparin
C) Alteration of T_4 and T_3 Metabolism with Modified Serum T_3 and T_4 Levels but Not TSH Levels;	
Increased hepatic metabolism, enhanced degradation of thyroid hormone	Nicardipine, phenytoin, carbamazepine, Primidone, phenobarbital, rifampin, rifabutin, tyrosine kinase inhibitors (e.g., Sunitinib, Sorafenib, Imatinib), sertraline, quetiapine
Inhibition of 5'-deiodinase with decreased T_3, increased rT_3	Iopanoic acid, Ipodate, Amiodarone, β-blockers, Corticosteroids, Propylthiouracil, Flavonoids, Interleukin-6
D) Other Interactions	
Interference with T4 absorption from the gut	Oral bisphosphonates, Cholestyramine, Colesevelam, Colestipol, Chromium picolinate, Charcoal, Ciprofloxacin, Proton Pump Inhibitors, Sucralfate, Kayexalate, Raloxifene, Sevelamer hydrochloride, Aluminum hydroxide, Ferrous sulfate, Calcium carbonate, Bran/fiber, Soy, Coffee, Orlistat
Induction of autoimmune thyroid disease with hypothyroidism or hyperthyroidism	Interferon-α, Interleukin-2, Interferon-β, Lithium, Amiodarone, Tyrosine Kinase Inhibitors (e.g., Sunitinib, Sorafenib, Imatinib)

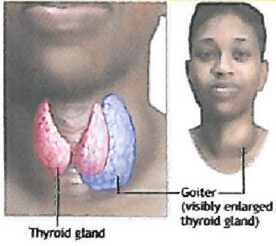
E) Effect of Thyroid Function on Drug Effects;

Drug	Hyperthyroidism	Hypothyroidism
Anticoagulation	Lower doses of Warfarin is required	Higher doses of Warfarin is required
Glucose Control	Increased hepatic glucose production and glucose intolerance	Impaired insulin action and glucose disposal
Cardiac Drugs	Higher doses of Digoxin is required	Lower doses of Digoxin is required
Sedatives and Opioids	Decreased sedative and respiratory depressant effects	Increased sedative and respiratory depressant effects

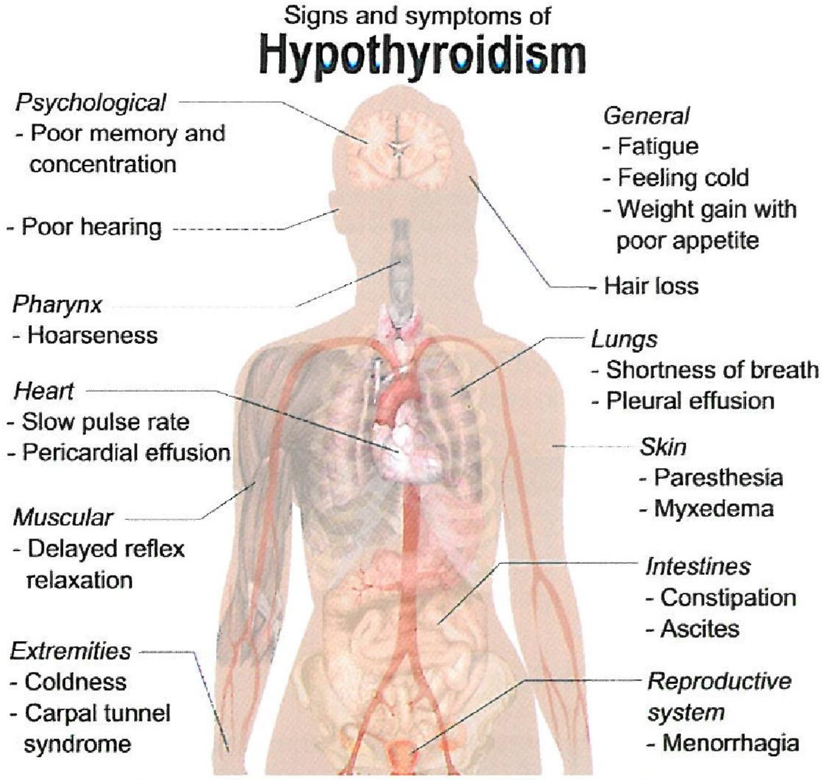
Table from; Basic and Clinical Pharmacology 14th edition, Katzung-Lange

Disturbance of Thyroid Gland Function

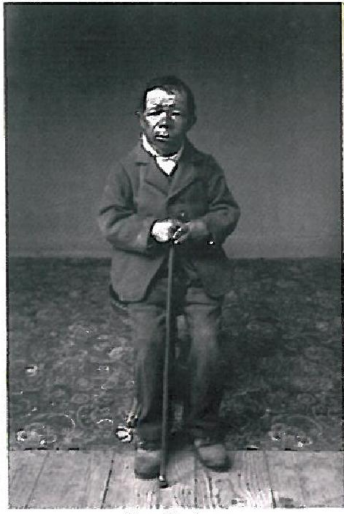
Hypothyroidism


Goiter (visibly enlarged thyroid gland)
Thyroid gland

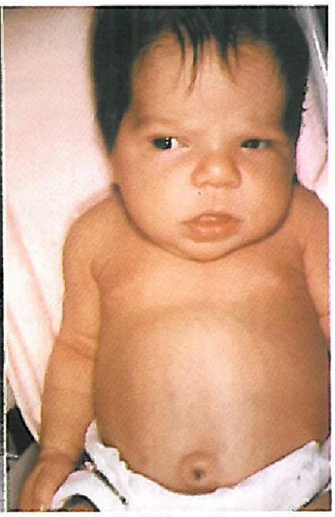
- **Hypothyroidism** is a *condition* in which **thyroid gland** ***does not*** **produce** a ***sufficient*** **amount** of the **thyroid hormones** T_4 and T_3.
- **Hypothyroidism** in **infants** and **children**, there is ***striking*** **retardation** of **growth** and **development** that ***results in*** **dwarfism** and ***irreversible*** **mental retardation**.
- **Hypothyroidism** can **occur** ***with*** or ***without*** **Thyroid Enlargement** (**Goiter**).
- ***Diagnosis*** of **hypothyroidism** in the adult is *easily* made by the ***combination*** of ***low*** **free thyroxine** and ***elevated*** **serum TSH** ***levels***.
- ***Most common*** **cause** is *probably* **Hashimoto's thyroiditis.**
- ***Common Causes***;
  - A) **Primary** (**Thyroid Gland**);
    - **Autoimmune disease** (**Hashimoto's Thyroiditis**; **thyroid gland** is ***gradually*** **destroyed**).
    - ***Congenital*** **absence** of **thyroid** (**Congenital Hypothyroidism**).
    - ***Defect*** in **synthesis** of **thyroid hormones.**
    - ***Excessive*** **administration** of **anti-thyroid drugs.**
    - ***Chronic*** **iodine deficiency.**
    - **Radiation therapy.**
    - **Drugs**; such as **Lithium**, **Amiodarone** and **Tyrosine Kinase Inhibitors** (such as **Sunitinib**).
  - B) **Secondary** (**Pituitary**); ***Not*** **produce** *enough* **TSH**.
  - C) **Tertiary** (**Hypothalamus**); ***Not*** **produce** *enough* **TRH**.


Signs and symptoms of
Hypothyroidism
Psychological
- Poor memory and concentration
- Poor hearing
Pharynx
- Hoarseness
Heart
- Slow pulse rate
- Pericardial effusion
Muscular
- Delayed reflex relaxation
Extremities
- Coldness
- Carpal tunnel syndrome
General
- Fatigue
- Feeling cold
- Weight gain with poor appetite
Hair loss
Lungs
- Shortness of breath
- Pleural effusion
Skin
- Paresthesia
- Myxedema
Intestines
- Constipation
- Ascites
Reproductive system
- Menorrhagia

- **Congenital Hypothyroidism**;
  - ***Signs*** and ***Symptoms***;
    - Myxedematous facies.
    - Large tongue (Macroglossia).
    - Umbilical hernia.
    - Wide nasal bridge.
    - Exaggerated jaundice.
    - Low body temperature.
    - Excessive sleeping.
    - Reduced interest in nursing.
    - Poor muscle tone, low or hoarse cry.
    - Infrequent bowel movements.
  - By **several years** of **age**, they would *display* the *recognizable* **facial** and **body features** of **cretinism**.



Cretinism



Congenital Hypothyroidism

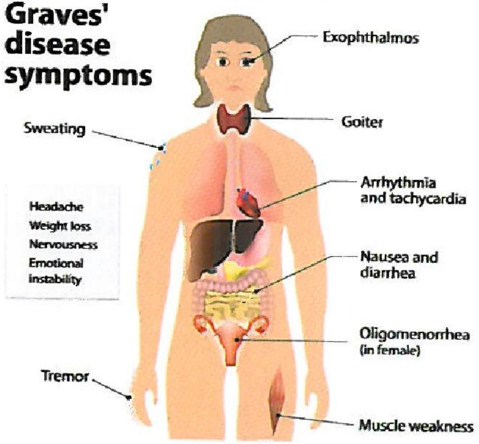
- **Myxedema**; is a **dermatological** ***change*** that can occur in **hypothyroidism** and ***some forms*** of **hyperthyroidism**, it is occur due to ***deposition*** of **muco-polysaccharides** in the **dermis**, which **results** in **swelling** of the **affected area**; **texture** of the *skin* may be ***similar to*** that of an **"orange peel"**.
- **Myxedema Coma** or **Myxedema Crisis**; is a *rare* **life-threatening** ***clinical condition*** that **represents** ***severe*** **hypothyroidism** with **physiological decompensation**.

Hyperthyroidism

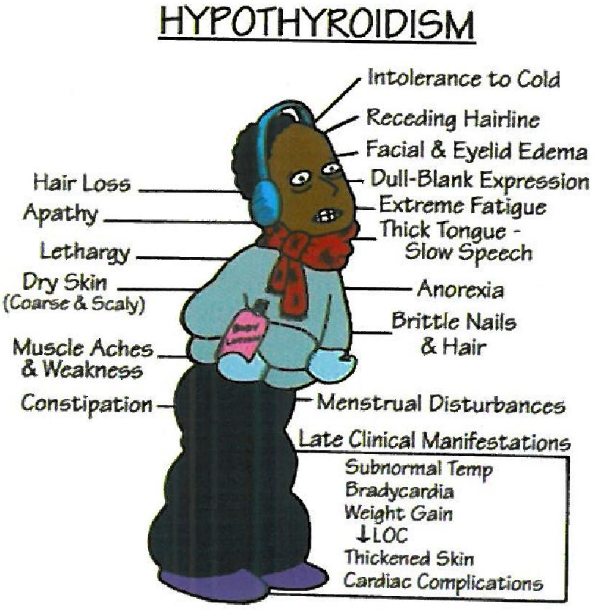
- **Hyperthyroidism** is the **condition** that *occurs* *due to* *excessive* **production** of **thyroid hormone** by the **thyroid gland**.
- **Thyrotoxicosis**, which *refers to* an *excessive* **amount** of *circulating* **thyroid hormone**, is *not synonymous with* **hyperthyroidism**.
- The *most* **common** *forms* of **hyperthyroidism** is **Graves' disease** (**toxic diffuse goiter**); is an **autoimmune disease** that *affects* the **thyroid**.
- **Graves' ophthalmopathy** is the *most common signs* in **Graves' disease** *include* **bulging eyes** (**exophthalmos**), *redness* and *retracting* **eyelids**.
- *Signs* and *symptoms* of **Hyperthyroidism** *vary between* **people** and may *include*; **nervousness**, **irritability**, **muscle weakness**, **anxiety**, **difficulty sleeping**, a **fast heartbeat**, **heat intolerance**, **diarrhea**, *enlargement* of **thyroid** (**Goiter**) and **weight loss**.

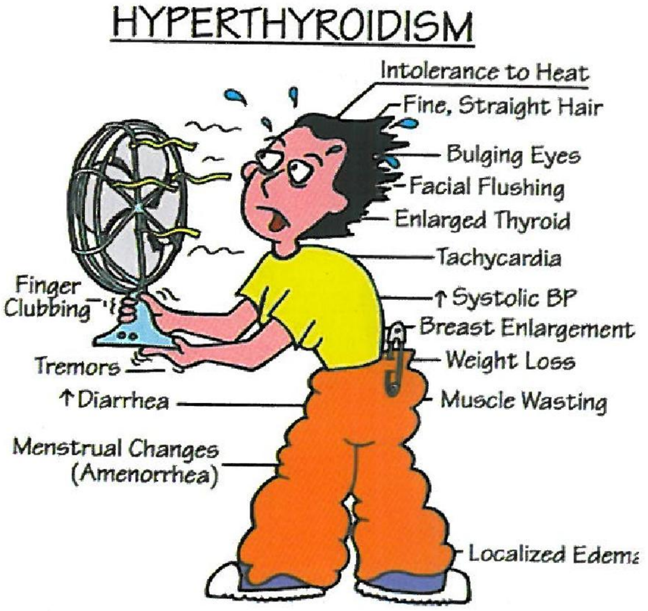
Enlarged thyroid
Normal size
Bulging eyes
Goiter

- **Thyroid Storm**; is a *severe* **form** of **thyrotoxicosis** *characterized by* **rapid** and *often* **irregular heartbeat**, *high* **temperature**, **vomiting**, **diarrhea** and **mental agitation**.
- **Postpartum Thyroiditis** (**PPT**) occurs in *about* **5%** of **women** *during* the **year** *after* they give birth, *usually* **corrects** *itself* *within* **weeks** or **months** *without* the *need* for **treatment**.
- *Major* *Causes* of **Hyperthyroidism**;
  - **Graves' Disease**; An **autoimmune disease** (most common with 50-80% worldwide); *produce* **antibodies** that *mimic* the **TSH** *effects* (antibodies activate thyroid gland TSH receptors).
  - **Toxic Multinodular Goiter**; is a *multinodular* **goiter** *associated with* **hyperthyroidism**.
  - **Toxic Thyroid Adenoma**; is a **benign tumor** of the **thyroid gland**.
- *Management* of **Hyperthyroidism**;
  - A) **Antithyroid Drug Therapy**; *see next.*
  - B) **Radioactive Iodine**; *see next.*
  - C) **Thyroidectomy**; is the *treatment of choice* for **patients** with *very* **large glands** or **multinodular goiters**.
  - D) **Adjuncts to Antithyroid Therapy**; *such as* **Propranolol** (β-blocker) OR **Diltiazem** (calcium channel blocker) to *control* **tachycardia**.


Graves' disease symptoms
Exophthalmos
Goiter
Sweating
Arrhythmia and tachycardia
Headache
Weight loss
Nervousness
Emotional instability
Nausea and diarrhea
Oligomenorrhea (in female)
Tremor
Muscle weakness

- **Hyperthyroidism** *vs* **Hypothyroidism**;

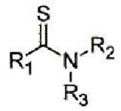

HYPOTHYROIDISM
Intolerance to Cold
Receding Hairline
Facial & Eyelid Edema
Dull-Blank Expression
Extreme Fatigue
Thick Tongue - Slow Speech
Hair Loss
Apathy
Lethargy
Dry Skin (Coarse & Scaly)
Anorexia
Brittle Nails & Hair
Muscle Aches & Weakness
Constipation
Menstrual Disturbances
Late Clinical Manifestations
Subnormal Temp
Bradycardia
Weight Gain
↓LOC
Thickened Skin
Cardiac Complications


HYPERTHYROIDISM
Intolerance to Heat
Fine, Straight Hair
Bulging Eyes
Facial Flushing
Enlarged Thyroid
Tachycardia
↑ Systolic BP
Finger Clubbing
Breast Enlargement
Tremors
Weight Loss
↑ Diarrhea
Muscle Wasting
Menstrual Changes (Amenorrhea)
Localized Edem

Antithyroid Agents

Thioamides (Thyroid Peroxidase Inhibitors)

- **Thioamides** are ***major drugs*** for **treatment** of **Thyrotoxicosis** and **Hyperthyroidism**.
- **Thioamides** are ***relatively*** **simple molecules** which ***contain*** a **sulfhydryl group** and a **thiourea moiety** ***within*** a **heterocyclic structure**.
- ***Most common*** **Thioamides** are; **Propylthiouracil**, **Methimazole** and **Carbimazole** (**Methimazole** ***pro-drug***).



General structure of a thioamide

Propylthiouracil (PTU) (Thyrocil®) | Methimazole (Tapazole®)

Carbimazole (Neo-mercazole®)

- **Propylthiouracil** [proe-pil-thye-oh-YOOR-ah-sil] (**PTU**) and **Methimazole** [me-THIM-ah-zole] are ***major drugs*** for **treatment** of **Thyrotoxicosis**.
- **Carbimazole** [KAR-beem-ah-zole] is a ***pro-drug*** of **Methimazole** that is **used *only*** in **Europe**, **Australia** and ***other*** **countries** (not USA).
- **Methimazole** is about **10 times** ***more potent*** than **Propylthiouracil** and is the ***drug of choice*** in **adults** and **children** (*due to* **Propylthiouracil** has ***high*** **risk** of **hepatotoxicity**).

Pharmaco Kinetics

	Propylthiouracil	Methimazole
Absorption	Rapidly absorbed	Completely absorbed but at variable rates
Bioavailability	50-80% (incomplete /large first-pass effect)	80-90%
Metabolism	Liver (primary by glucuronidation)	
Excretion	Kidney	Kidney (*slower than* Propylthiouracil)
Plasma Protein Binding	80-90% is bound to albumin	None or minimal (free in serum)
Half-life	*Short* half-life (1.5 hours) *but* accumulated by the thyroid; dosing interval *every* 6–8 hours.	6 hours *and* accumulated by the thyroid; dosing interval *every* 24 hours.
Pregnancy	Crosses placental barrier	

Mechanism OF Action

- ***Major*** ***Mechanism***; ***Inhibit*** **thyroid peroxidase enzyme** and ***blocking*** **iodine organification** → ***prevent*** **hormone synthesis**.
- ***Other*** ***Mechanisms***;
  - ***Block*** **coupling** of the **Iodotyrosines**.
  - **Propylthiouracil** (***not*** **Methimazole**) also ***inhibits*** the **peripheral deiodination** of **T_4** and **T_3**.
- **N.B.**; The ***onset*** ***of*** ***action*** **these agents** is ***slow***, ***often requiring* 3–4 weeks *before*** **stores** of **T_4** are ***depleted***.

- **Propylthiouracil** and **Methimazole** are ***classified as*** **FDA pregnancy category D** (***risk*** of **fetal hypothyroidism**); ***Caution*** **must** be ***employed*** when ***using*** these **drugs** in **pregnancy**.
- **Propylthiouracil** is ***preferable during*** the **first trimester** of **pregnancy** because it is ***more strongly*** **protein-bound** and therefore, ***crosses*** the **placenta** ***less*** **readily** (**Methimazole** *may* **use** in **2nd** and **3rd trimesters**).
- **Propylthiouracil** and **Methimazole** are ***secreted*** in ***low*** **concentrations** in **breast milk** *but* are **considered** ***safe*** for the **nursing infant**.

Side Effects

- **Skin** (***Most*** ***common*** **side effects**); **Dermatologic reactions** *with* **fever**.
- **GIT** (Occur early); **Nausea** and **GI distress**.
- **Liver**; - **Severe hepatitis** *with* **Propylthiouracil** (**black box warning**).
  - **Cholestatic jaundice** (*commonly with* **Methimazole**).
- **Blood** (***Dangerous*** **complication**; ***rarely*** but **fatal**); **Agranulocytosis**.

Anion Inhibitors (Sodium-iodide Symporter Inhibitors)

- **Monovalent anions** such as **Perchlorate** (ClO_4^-), **Pertechnetate** (TcO_4^-) and **Thiocyanate** (SCN^-) can ***block*** **uptake** of **Iodide** by the **gland** through ***competitive*** **inhibition** of the **iodide transport**.

Potassium Perchlorate (Perchloracap®)

- **Potassium perchlorate** is ***rarely*** **used** (*associated with* **aplastic anemia**).
- It ***block*** **thyroidal reuptake** of I^- in *patients with* **Iodide-*induced* Hyperthyroidism** such as **Amiodarone-*induced* Hyperthyroidism**.

Iodide Therapy (Blockade of Hormone Release)

Lugol's Iodine

Potassium Iodide

- **Iodide Therapy** is ***rarely*** **used** *today*.
- **Lugol's iodine** is a ***solution*** of **Potassium Iodide *with* Iodine** in **water**; *used as* **Disinfectant** and for **Thyrotoxicosis** and as **preoperative preparation** for **surgery** (***decrease*** the **vascularity**, **size**, and **fragility** of a **hyperplastic gland**); ***not useful*** for **long-term therapy**, because the **thyroid** ceases to ***respond*** to the **drug *after*** a ***few*** **weeks** (**Jod-Basedow effect**).
- ***Mechanism of Actions***; ***several*** **actions**;
  - ***Major*** **action**; ***Inhibition*** of **hormone release**.
  - ***Other*** **actions**; ***Inhibit*** **organification**, ***decreased*** **thyroidal size** and **vascularity**.
  - ***Improvement*** in **thyrotoxic symptoms** occurs ***rapidly***; *within* **2-7 days**.
- ***Toxicity*** (**Iodism**); are ***uncommon*** and ***reversible*** upon **discontinuance**; acneiform rash, swollen salivary glands, mucous membrane ulcerations, conjunctivitis, rhinorrhea, drug fever, metallic taste, bleeding disorders and rarely, anaphylactoid reactions.

Radioactive Iodine (RAI) - Iodine-131 (^{131}I)

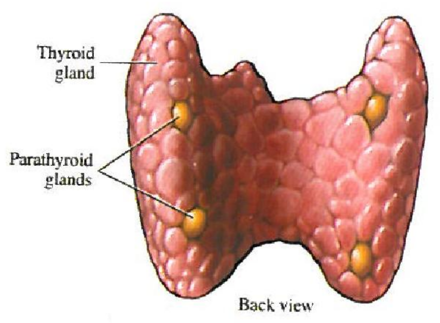
- ^{131}I is the ***only*** **isotope** ***used for treatment*** of **Thyrotoxicosis** and ***some types*** of **thyroid cancer** that ***absorb*** **Iodine**.
- ^{131}I ***rapidly*** **absorbed**, ***concentrated*** in the **thyroid follicles** → *radioactive* **Iodine *becomes*** **toxic** to **cells** (***emission of*** **β rays**) → **thyroid parenchymal *destruction*** *occurs* ***within*** a **few weeks**.
- ***Therapeutic Advantages*** for ^{131}I;
  - ***Good*** **efficacy**.
  - ***Low*** **expense**.
  - ***Easy*** **administration**.
  - ***Absence*** of **pain**.
- ***Contraindications***; **Pregnant women** or **nursing mothers** (it crosses the placenta to destroy the fetal thyroid gland and it is excreted in breast milk).

Others

- **Ipodate** and **Iopanoic acid** are **Iodine-*containing* radiocontrast medium**, they are ***inhibit*** **peripheral conversion** of T_4 to T_3 and may ***decrease*** T_4 ***synthesis*** **used *off-label*** in **hyperthyroidism**.
- **β-blockers** *such as* **Propranolol**, are ***effective*** to ***control*** **sympathetic *stimulation*** that **occurs** in **hyperthyroidism** (it also ***reduce*** T_3 levels by ***inhibiting*** the **peripheral conversion** of T_4 to T_3).

Parathyroid Hormones

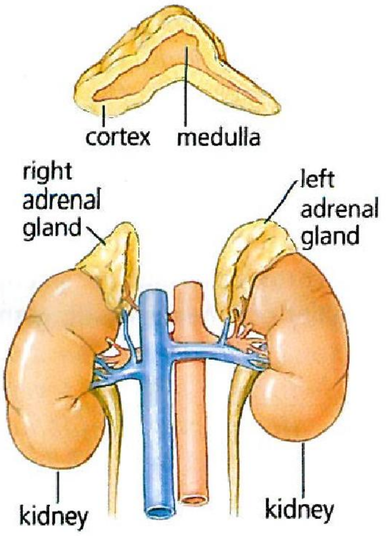
- **Parathyroid glands** are ***small*** **endocrine glands** in that ***produce*** **Parathyroid Hormone** (**PTH**).
- **Humans** usually have **4 parathyroid glands**, variably ***located*** on the **back** of the **thyroid gland**.
- **Parathyroid Hormone** (**PTH**) and **Calcitonin** (***produced by*** **C-cells** in **thyroid gland**) have **key roles** in ***regulating*** the ***amount*** of **Calcium** in the **blood** and ***within*** the **bones**.
- **Hyperparathyroidism** and **hypoparathyroidism**, *characterized by* ***alterations*** in the **blood Calcium *levels*** and **bone metabolism**,

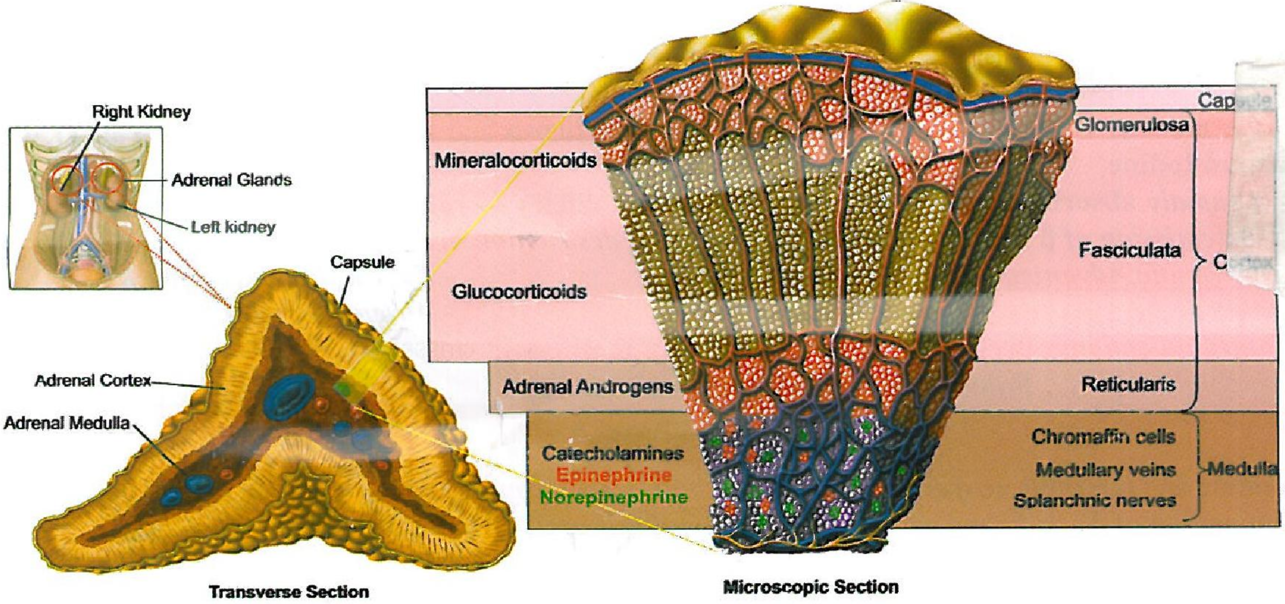


- **Bone Metabolism**, **Parathyroid Hormone** (**Teriparatide**) and **Calcitonin Hormone** are was ***fully*** **discussed** in **Osteoporosis** ***topic*** in **Bone & Joint Chapter**.

Adrenocortical Hormones

- **Adrenocortical hormones** are **hormones** ***produced by*** the **adrenal cortex**, the ***outer region*** of the **adrenal gland**.
- **Adrenal Glands** (**suprarenal glands**) are **endocrine glands** that sit at the **top** ***of*** the **kidneys**.
- **Adrenal Gland** ***consist of*** **2 distinct parts**;
  1) **Adrenal Cortex** (**Outer Zone**); *about* **80%** of the **gland**.
     - ***Producing*** **Steroid Hormones**; **Aldosterone**, **Cortisol** & ***Adrenal*** **Androgens**.
  2) **Adrenal Medulla** (**Inner Zone**); *about* **20%** of the **gland**.
     - ***Producing*** **Catecholamines**; **80% Adrenaline** & **20% Noradrenaline**.
- **Adrenal Cortex** is ***formed*** by **3 layers**;
  1) **Zona Glomerulosa** (**Outer layer**); *about* **15%** of the **cortex**;
     - ***Producing*** **Mineralocorticoids**; **Aldosterone**.
  2) **Zona Fasciculata** (**Middle layer**); *about* **75%** of the **cortex**;
     - ***Producing*** **Glucocorticoids**; such as **Cortisol**.
  3) **Zona Reticularis** (**Inner layer**); *about* **10%** of the **cortex**;
     - ***Producing*** ***Adrenal*** **Androgens** such as **Dehydroepiandrosterone (DHEA)**, **DHEA sulfate** and **Androstenedione** (*precursor* to **Testosterone**).

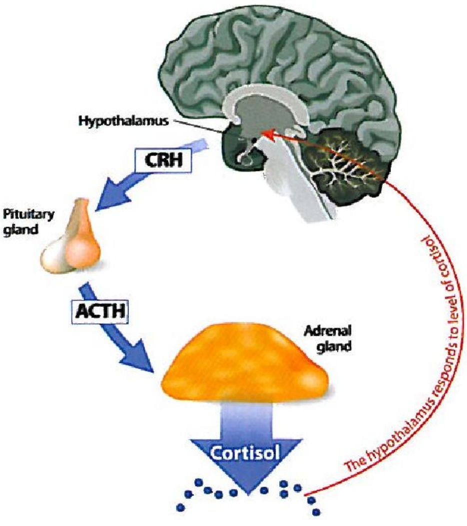

cortex
medulla
right adrenal gland
left adrenal gland
kidney
kidney

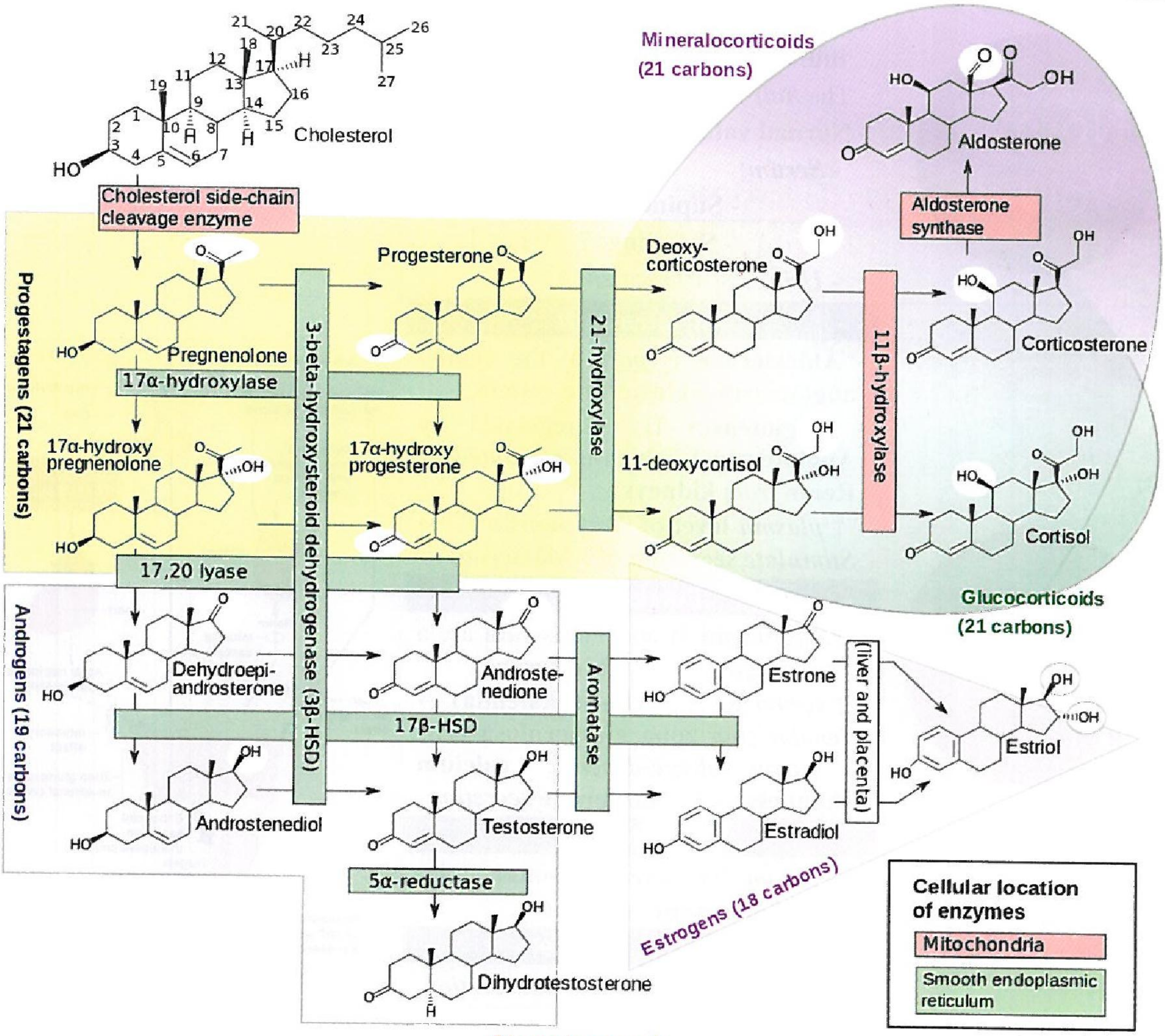

Right Kidney
Adrenal Glands
Left kidney
Capsule
Adrenal Cortex
Adrenal Medulla
Mineralocorticoids
Glucocorticoids
Adrenal Androgens
Catecholamines
Epinephrine
Norepinephrine
Cap
Glomerulosa
Fasciculata
C
Reticularis
Chromaffin cells
Medullary veins
Splanchnic nerves
Medulla

Transverse Section

Microscopic Section

- **Adrenocortical Hormones** (***primary*** **Glucocorticoids**) are ***controlled by*** **pituitary Adrenocorticotropic Hormone (ACTH)**, *which* is ***released*** in ***response to*** **hypothalamic Corticotropin-releasing Hormone (CRH)**.
- **Glucocorticoids** *serve as* **feedback inhibitors** of **ACTH** and **CRH** ***secretion***.
- A ***number*** of **endocrine diseases** involve ***dysfunctions*** of the **adrenal gland**;
  - ***Overproduction*** of **Cortisol** *leads to* **Cushing's syndrome**.
  - ***Insufficient*** **production** of **Adrenocortical Hormones** *leads to* **Addison's disease**.
- **Adrenocortical Hormones** are ***considered*** **Steroid Hormones** because of the ***shared*** **characteristic** of a **Cholesterol** ***backbone***.


Hypothalamus
CRH
Pituitary gland
ACTH
Adrenal gland
Cortisol
The hypothalamus responds to level of cortisol


Cholesterol
HO
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
17α-hydroxylase
17α-hydroxy pregnenolone
17,20 lyase
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
Progesterone
17α-hydroxy progesterone
21-hydroxylase
Deoxy-corticosterone
11-deoxycortisol
11β-hydroxylase
Corticosterone
Cortisol
Aldosterone synthase
Aldosterone
Mineralocorticoids (21 carbons)
Glucocorticoids (21 carbons)
Androgens (19 carbons)
Dehydroepi-androsterone
Androstenediol
Androste-nedione
17β-HSD
Testosterone
5α-reductase
Dihydrotestosterone
Aromatase
Estrone
Estradiol
(liver and placenta)
Estriol
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Steroidogenesis

Mineralocorticoids

Aldosterone

- **Mineralocorticoids** are a *class* of **Steroid Hormones** *characterized by* their ***influence*** on **salt** and **water *balances*.**
- The ***name*** **Mineralocorticoid** *derives from* early *observations* that these **hormones** were ***involved in*** the ***retention*** of **Sodium**, a **mineral**.
- The ***primary*** **mineralocorticoid** is **Aldosterone.**
- *Other* ***endogenous*** **hormones** such as **Progesterone** & **Deoxycorticosterone** have **mineralocorticoid *function*.**
- **Aldosterone** is ***produced*** in the **zona glomerulosa** of the **cortex** of the **adrenal gland.**
- **Aldosterone *secretion*** is *mediated* ***primary*** by **Angiotensin II *but*** also by **Adrenocorticotrophic Hormone** (**ACTH**) and ***local*** **Potassium *levels***;
  - **Angiotensin II** → **Adrenal Cortex** → **Aldosterone.**
  - **Angiotensin II** → **Posterior Pituitary** → **Antidiuretic Hormone** (**ADH**).
- **ACTH** has ***only*** a ***minor*** **role** in ***regulating*** **Aldosterone *production*** (**Angiotensin II** is the ***major*** **role**);
  - ***Without*** **ACTH**, **Aldosterone *secretion*** **falls** to *about* **half** the **normal rate.**
- **Mineralocorticoids** (***primary*** **Aldosterone**) ***plays*** a ***major role*** in the **homeostatic *regulation*** of **blood pressure**, ***plasma*** **sodium** (**Na^+**) and **potassium** (**K^+**) ***levels***.

Normal Values

- **Aldosterone** is *secreted* at the rate of **100–200 mcg/d** in ***normal*** **individuals** with a ***moderate*** **dietary salt intake.**
- The ***half-life*** of **Aldosterone** is **15–20 minutes.**
- **Normal values** of **Aldosterone** in adult;
  - ***Serum***;
    - **Supine** (*resting*); 3–16 ng/dL.
    - **Standing**; 7–30 ng/dL.
  - ***Urine***; 3–19 mcg/24 h.

Regulation

Angiotensin II

- **Aldosterone** is ***part*** of the **renin–angiotensin–aldosterone system.**
- **Angiotensin II** is regulated by **Angiotensin I**, which is ***regulated by*** **Renin** *from* **kidneys.**
- ↑ ***plasma*** **level** of **Angiotensin II** → ***Stimulate*** **secretion** of **Aldosterone.**

Potassium

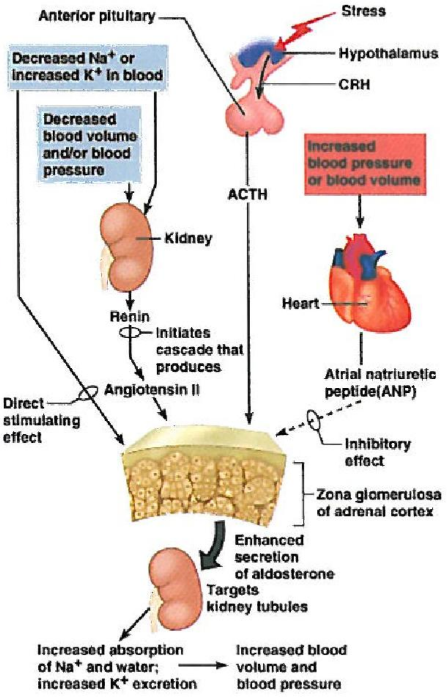
- **Angiotensin II** and **Potassium** are a ***secretagogues*** for **Aldosterone.**
- ↑ ***serum*** K^+ ***level*** (**Hyperkalemia**) → ***depolarizing*** **zona glomerulosa cells** → ***opens voltage-dependent*** **calcium channels** → ↑ **Aldosterone *secretion.***

Sodium

- ↓ ***serum*** Na^+ ***level*** (**Hyponatremia**) → ↑ **Aldosterone *secretion.***

ACTH (minor *role*)

- ↑ **ACTH** → ↑ **Aldosterone *secretion.***


Anterior pituitary
Stress
Hypothalamus
CRH
Decreased Na+ or increased K+ in blood
Decreased blood volume and/or blood pressure
ACTH
Increased blood pressure or blood volume
Kidney
Heart
Renin
Initiates cascade that produces
Angiotensin II
Atrial natriuretic peptide(ANP)
Direct stimulating effect
Inhibitory effect
Zona glomerulosa of adrenal cortex
Enhanced secretion of aldosterone
Targets kidney tubules
Increased absorption of Na+ and water; increased K+ excretion
Increased blood volume and blood pressure

Mechanism OF Action

- **Mineralocorticoids** *such as* **Aldosterone** ***binds*** to **cytoplasmic Mineralocorticoid Receptors** (**MR**), and ***activated*** **receptors** ***affect*** **gene transcription** (***genomic mechanism***) → the ***major effect*** is ***increased*** **expression** of **Na^+/K^+-ATPase** and ***epithelial*** **sodium channel** (**ENaC**).
- The **MR** is ***stimulated by*** ***both*** **Aldosterone** and **Cortisol**, ***but***;
  - An ***enzyme called*** **11β-hydroxysteroid dehydrogenase** (**11β-HSD**) ***type 2*** in the **kidney** which ***converts*** **Cortisol** to **Cortisone**; **Cortisone** has ***little*** **affinity** for the **MR** → **prevent** *excess* **Aldosterone receptor stimulation.**
  - **Liquorice**, which ***contains*** **Glycyrrhetinic Acid**, can ***inhibit*** **11β-HSD** and ***lead to*** a **Mineralocorticoid Excess Syndrome**; **hypokalemia**, **hypertension** and **hypernatremia.**

Function

[***Reabsorption*** of Na^+, **water** and Cl^- - ***Excretion*** of K^+ and H^+]

1) ***Stimulates*** Na^+ and **water** ***reabsorption into*** the **blood** ***from*** the **distal convoluted tubule** and **collecting duct** of the **nephron** and ***stimulates*** K^+ ***secretion into*** the **urine**; via ***activation*** of **Na^+/K^+ pumps** and **conformational change** in the **pump** to ***exposes*** the **Na^+ ions.**
   - **N.B**; Cl^- is ***reabsorbed*** in ***conjunction with*** Na^+ to ***maintain balance.***
2) ***Stimulates*** H^+ ***secretion***; via the **H^+/ATPase.**
3) ***Stimulates*** Na^+ and **water** ***reabsorption*** from the **gut**, **salivary** and **sweat glands** in *exchange* for K^+.

Disturbance of Mineralocorticoids Function

Hyperaldosteronism

- **Primary Hyperaldosteronism** (**Conn's syndrome**); is ***excess*** **production** of the **Aldosterone**, ***most commonly*** *caused by* an **adrenal adenoma**.
- **Secondary Hyperaldosteronism**; is due to ***overactivity*** of **renin–angiotensin–aldosterone system**.
- ***Excessive*** levels of **Aldosterone** or **overdosage** with ***synthetic*** **mineralocorticoids** *lead to* **Hypokalemia**, **Metabolic Alkalosis**, **Hypernatremia** and **Hypertension**.

Hypoaldosteronism

- **Hypoaldosteronism** is ***underproduction*** of **Aldosterone**, *leads to* the **salt-wasting state** *associated with* **Addison's disease**, **congenital adrenal hyperplasia** and ***other*** **disease states**.
  - **Addison's Disease**; **adrenal glands *do not*** **produce** *enough* **steroid hormones** (**Cortisol**, **Aldosterone** and **Adrenal Androgens**), most often *due to* **adrenal glands *damage*** by the **immune system**.
  - **Congenital Adrenal Hyperplasia** (**CAH**); is ***mutations*** of **genes** *for* **enzymes** *mediating* the **biochemical steps** of ***production*** **adrenal hormones**;
    - Inefficient cortisol production results in rising levels of ACTH via feedback inhibition → stimulation induces overgrowth (hyperplasia) and overactivity of the steroid-producing cells of the adrenal cortex → increased levels of adrenal androgens.
    - The treatment is to administer a glucocorticoid, such as hydrocortisone (in infants) or prednisone, which would restore the feedback inhibition.

Other/Synthetic Mineralocorticoids

Deoxycorticosterone (DOC)

- **Deoxycorticosterone** (**DOC**) or **Desoxycorticosterone** or **Desoxycortone** which also ***serves as*** a ***precursor*** of **Aldosterone**.
- **DOC** ***secretion*** is **primarily under** the ***control*** of **ACTH** (**Angiotensin II** has ***little effect*** on **DOC**).
- **DOC** is ***normally*** **secreted** in amounts of *about* **200 mcg/day**.
- **Deoxycorticosterone Acetate** (**DOCA**) or **Deoxycorticosterone Pivalate** (**DOCP**) are **currently** available as **IM injection** for **use** ***only*** in ***animals*** (**Dogs** and **Cats**) to ***treat*** **Adrenocortical Insufficiency** and **Addison's Disease**.

Fludrocortisone (Astonin-H®)

- **Fludrocortisone** [floo-droe-KOR-ti-sone] (**9α-fluorocortisol** or **9α-fluorohydrocortisone**) is a ***synthetic potent*** **mineralocorticoid** (250 parts salt-retaining) with ***some*** **glucocorticoid** ***activity*** (10 parts anti-inflammatory). **Fludrocortisone** is the ***most widely*** used **mineralocorticoid**.
- **Fludrocortisone Acetate** is ***used*** **orally** to ***treat*** **Adrenocortical Insufficiency/Addison's Disease**, **Congenital Adrenal Hyperplasia** and **Postural Hypotension** (*off-label*).
- **Fludrocortisone** is also **used** in ***confirmation test*** for **diagnosing Conn's syndrome**.
- ***Usual Dose***; **0.1 mg/day *orally***.
- ***Side effects***; **Hypertension**, **edema**, **heart failure** and **hypokalemia**.

Mineralocorticoids Antagonists

Spironolactone (Aldactone®)

Eplerenone (Inspra®)

- **Spironolactone** [speer-on-oh-LAK-tone] is a ***synthetic*** **steroid** that *acts as* a **competitive antagonist** to **Aldosterone** at **mineralocorticoid receptors**. **Eplerenone** [eh-PLEH-reh-none] is a **Spironolactone** ***analogue*** with much ***greater*** **selectivity** for the **mineralocorticoid receptors**.
- **Eplerenone** has a ***several*** **hundredfold** ***less active*** on **androgen** and **progesterone receptors** than **Spironolactone**, therefore, **Eplerenone** has considerably ***fewer*** **side effects**.
- **Spironolactone** ***uses***; **Primary hyperaldosteronism** (**Conn's syndrome**), **Edema**, **Essential hypertension**, **Hypokalemia** and **Antiandrogen** (**hirsutism**, **acne** in ***women*** & **androgenic alopecia**).
- **Eplerenone** ***uses***; **Congestive heart failure post-myocardial infarction** and **Hypertension**.
- ***Side effects***; **hyperkalemia**, **metabolic acidosis** and **endocrine abnormalities** (*with* **Spironolactone**; **gynecomastia**, **impotence** and **menstrual irregularities**).

Glucocorticoids (GC)

Short Acting (<12 hours)	
Cortisol (**Hydrocortisone**) (Solu-Cortef®)	**Cortisone** (Cortone Acetate®)
Intermediate Acting (12-36 hours)	
Prednisone (Hostacortin®)	**Prednisolone** (Hostacortin-H®)
Triamcinolone (Kenacort-A®)	**Methylprednisolone** (Solu-Medrol®)
Long Acting (>48 hours)	
Betamethasone (Diprofos®)	**Dexamethasone** (Dexamethasone®)

- The ***name*** **Glucocorticoid** (**gluco**se + **cort**ex + ster**oid**) is ***composed from*** its **role** in ***regulation*** of **Glucose** ***metabolism***, ***synthesis*** in the **adrenal cortex** and its **steroidal** ***structure***.
- **Glucocorticoids** are **essential** ***for*** **life**; they are ***regulates*** or ***supports*** a *variety* of ***important*** **cardiovascular**, **metabolic**, **immunologic** and **homeostatic** ***functions***.
- **Cortisone** was ***first*** **produced** ***commercially*** by **Merck & Co.** in **1948** (or 1949).
  - Tadeusz Reichstein, Edward Calvin Kendall and Philip Showalter Hench were awarded the Nobel Prize for Physiology and Medicine in 1950 for their work on hormones of the adrenal cortex, which culminated in the isolation of cortisone.
- **Cortisol** or **Hydrocortisone** [hye-droe-KOR-tih-sone] and **Cortisone** [KOR-tih-sone] are ***naturally*** *occurring* **Glucocorticoids**.
- **Prednisone** [PRED-nih-sone], **Prednisolone** [pred-NIH-so-lone], **Triamcinolone** [trye-am-SIN-oh-lone], **Methylprednisolone** [METH-il-pred-NIS-oh-lone], **Betamethasone** [bay-ta-METH-a-sone] and **Dexamethasone** [dex-a-METH-a-sone] are ***synthetic*** **Glucocorticoids**.
- **Prednisone** is a ***prodrug*** that ***converted to*** **Prednisolone**, the **active compound** in the **liver**.
- **Hypothalamic-pituitary-adrenal axis**, **circadian rhythm**, **stress** and ***low blood*** **glucose** ***level*** are the ***most important*** **factors** in **glucocorticoids** ***secretion*** **regulation**.
  - ***Plasma*** **ACTH** & **Cortisol** ***levels*** *exhibit* **↑ peaks (6-8 AM)** & **↓ nadirs (11 PM)**.
- *Approximately* **90%** of **Cortisol** is ***bound*** to **Cortisol-binding Globulin** (**CBG**), *while* **5–10%** is ***bound*** to **Albumin** and ***only*** **5%** of ***circulating*** **Cortisol** is **free** to ***exert*** its **effect** on **target cells**;
  - If **CBG** is ***saturated*** (**Cortisol > 20–30 mcg/dL**) the ***concentration*** of **free Cortisol** ***rises*** **rapidly**.
  - **CBG** is ***increased*** in; **Pregnancy**, **Estrogen** and **Hyperthyroidism**.
  - **CBG** is ***decreased*** in; **Hypothyroidism**, **Genetic Defects** in ***synthesis*** and **Protein Deficiency** ***states***.

Normal Values

- ***Serum*** **Cortisol** ***Normal*** ***Values***;
  - ***Morning***; **7-28 mcg/dL.** - ***Afternoon***; **2-18 mcg/dL.**
  - *Low-dose* **ACTH Stimulation Test**; ***serum*** **Cortisol**; **≥ 18 mcg/dL.**
  - ***Overnight*** *low-dose* **Dexamethasone Suppression Test**; **8 AM** ***serum*** **Cortisol**; **< 1.8 mcg/dL.**

- **Brief** ***comparison*** *between* **Glucocorticoids** and **Mineralocorticoids**;

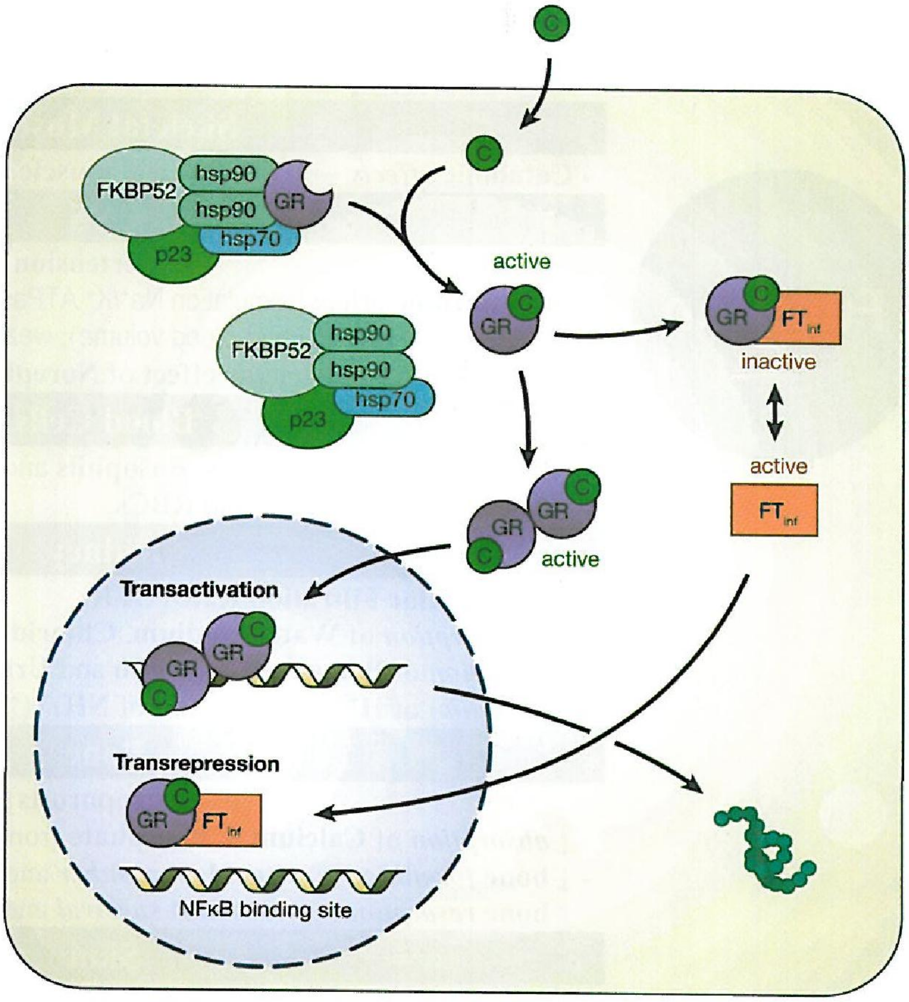
Agent	Activity			Equivalent Oral Dose (mg)	Forms Available
	Anti-Inflammatory	Topical	Salt-Retaining		
Cortisol	1	1	1	20	Oral, injectable, topical
Cortisone	0.8	0	0.8	25	Oral
Prednisone	4	0	0.3	5	Oral
Prednisolone	5	4	0.3	5	Oral, injectable
Methylprednisolone	5	5	0.25	4	Oral, injectable
Triamcinolone	5	5*	0	4	Oral, injectable, topical
Betamethasone	25-40	10	0	0.6	Oral, injectable, topical
Dexamethasone	30	10	0	0.75	Oral, injectable, topical
Fludrocortisone	10	0	250	2	Oral
Desoxycorticosterone	0	0	20		Injectable, pellets

- **Triamcinolone Acetonide**: ***Up to*** **100**

Table from; Basic and Clinical Pharmacology 14th edition, Katzung-Lange

- The **Cortisol** (**C**) is ***present*** in the **blood** in **bound form** on the **corticosteroid-binding globulin** (**CBG**) but ***enters*** the **cell** as the **free** ***molecule***.
- The ***intracellular*** **glucocorticoid receptor** (**GR**) is *bound to* **stabilizing proteins**, including **2 molecules** of **heat-shock protein 90** (**hsp90**) and ***several*** **others** including **FKBP5**. This **receptor complex** is ***incapable*** of **activating transcription**.
- When the **complex** ***binds*** a **molecule** of **Cortisol**, an ***unstable*** **complex** is ***created*** and the **hsp90** and **associated molecules** are ***released***.
- The **steroid-receptor complex** is ***now able to*** **dimerize**, **enter** the **nucleus**, ***bind*** to a **glucocorticoid response element** (**GRE**) on the ***regulatory region*** of the **gene**.
- A *variety* of **regulatory factors** may participate in ***facilitating*** (**coactivators**) or ***inhibiting*** (**corepressors**) the **steroid response**.
- The ***resulting*** **mRNA** is edited and exported to the cytoplasm for the ***production*** of **protein** that brings about the ***final*** **hormone response**.
- The **GR** also ***interacts*** with **nuclear factor kappa-B** (**NF-κB**), a ***regulator*** of **production** of **cytokines** and ***other*** **molecules** *involved in* **inflammation**.

Mechanism OF Action


C
C
FKBP52
hsp90
hsp90
GR
hsp70
p23
active
GR
C
FKBP52
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hsp90
hsp70
p23
GR
C
FTinf
inactive
active
FTinf
GR
GR
C
C
active
Transactivation
GR
GR
C
C
Transrepression
GR
C
FTinf
NFκB binding site

- **Two genes** for the **corticoid receptor** have been identified:
    - One *encoding* the classic **Glucocorticoid Receptor** (**GR**).
    - Other *encoding* the **Mineralocorticoid Receptor** (**MR**).
- A **mineralocorticoid effect** of the ***higher*** levels of **Cortisol** is ***avoided*** in **some tissues** (e.g., **kidney**, **colon**, **salivary glands**) by ***expression*** of **11β-hydroxysteroid dehydrogenase type 2** (**11β-HSD**) the **enzyme** ***responsible for*** **biotransformation** to **Cortisone**, which has ***minimal*** **action** on **Aldosterone** ***receptors***.

Function

Metabolism

Carbohydrate Metabolism (Hyperglycemic and Diabetogenic)

[**Steroid Diabetes**]

- *Stimulate* **gluconeogenesis** in the **liver**;
  - ↑ **amino acids** *uptake* by the **hepatic cell.**
  - ↑ *activity* of **enzyme** that *convert* **amino acid** *to* **glucose.**
- *Decrease* **insulin sensitivity** of **muscle** and **adipose tissue** (**Anti-insulin**);
  - ↓ *affinity* of **insulin receptor** to **insulin.**
  - ↓ **glucose** *transports* from the **cell membrane** to *inside* the **cell.**

* *Resistance* to **stress** → ↑ *serum* **glucose levels** to *maintenance* of an *adequate* **glucose** *supply* to the **brain.**

Protein Metabolism (Catabolic Effect)

- ↓ **protein** *synthesis* & ↑ **protein** *catabolism*.
- ↑ **plasma amino acid** *level*.
- ↓ **amino acid** *transport into* **extrahepatic tissues.**
- ↑ *conversion* of **amino acids** *into* **urea** (↑ *breakdown* of **amino acids**).

Fat Metabolism (Lipolytic and Ketogenic)

- ↑ **lipolysis** → ↑ **Free Fatty Acids (FFA)** in the **blood.**
- *Redistribution* of **fat** *depot* in the **facio-cervical-trunk region**; **moon face** and **buffalo hump** and in the **abdomen** → **purple striae** (*stretch marks*).

Skeletal Muscles

- **Catabolic** *effects* → **weakness** and **muscle atrophy** (↓ protein synthesis).

CVS

[**Hypertension**]

- **+ve inotropic** *effect* (stimulation Na^+/K^+ ATPase and of β-adrenergic receptors).
- **Na^+ & water** *retention* (↑ blood volume); weak mineralocorticoid effect.
- *Potentiate* **vasoconstrictor effect** of **Norepinephrine** and **Angiotensin II.**

Blood Cells

- ↓ **Lymphocytes, Monocytes, Basophils** and **Eosinophils.**
- ↑ **Neutrophils, Platelets** and **RBCs.**

Kidney

- ↑ **Glomerular Filtration Rate (GFR).**
- ↑ *reabsorption* of **Water, Sodium, Chloride.**
- ↑ *excretion* of **Potassium, Calcium** and **Uric Acid.**
- ↑ *excretion* of H^+ → ↑ *excretion* of NH_4^+ (↑ ammoniagenesis; H^+ + NH_3).

Bone

[**Osteoporosis**]

- ↓ *absorption* of **Calcium** & **Phosphate** from *intestine* (**Anti-vitamin D**).
- ↓ **bone** *formation*; ↓ **osteoblast** *number* and their *function*.
- ↑ **bone** *resorption*; ↑ **osteoclast** *survival* and *activity*.

Skin

- **Daily use of topical glucocorticoids for *several* weeks**

  [**Skin Atrophy** or **Steroid Atrophy** and **Skin Thinning**]

  - ↓ **collagen** *synthesis* by ↓ *proliferation* of **fibroblasts** → **thinning of skin** and *easy* **rupture.**

- **Daily use of topical glucocorticoids for *several* months or years**

  [**Topical Steroid Addiction; TSA**]

  - *When* **topical glucocorticoids** is ***stopped*** → **skin redness, burning, itching, hot skin** and **swelling** (**Red Skin Syndrome** or **Topical Steroid Withdrawal; TSW**).

Function

GIT

[**Steroid Ulcers**]

- **Ulcerogenic** ***effect***; - ↑ **gastric-acid** ***secretion***.
  - ↓ ***local*** **immune** ***response*** **against** ***H. pylori***.

Fetal Lung

[**Fetal Lung Maturation**]

- ↑ ***production*** of **surfactants** (***necessary*** for ***extra*** **uterine lung function**).
  - **SURVANTA**® (**Beractant**); **pulmonary surfactants** ***intratracheal injection***; used for **Respiratory Distress Syndrome** (**RDS**) (hyaline membrane disease) in ***premature*** **infants**.

CNS

- **Euphoria** and **behavioural** ***changes***.
- ***Maintenance*** of **alpha rhythm** in **electroencephalogram (EEG)**.
- ↓ **seizure** ***threshold***.
- ↑ ***intracranial*** **pressure (pseudotumor cerebri)**.

Eye

- **Glaucoma** (***due to increased*** **ocular pressure**) and **Cataracts**.

Anti-inflammatory Effects

- ***Suppress*** **Phospholipase A_2** ***activity*** (↓ arachidonic acid synthesis → ↓ prostaglandins and leukotrienes synthesis).
- ***Suppress*** **Cyclooxygenase (COX)** ***activity*** (↓ prostaglandins synthesis).
- ***Suppress*** **proinflammatory cytokines**, and ***other*** **inflammatory mediators** ***release***; such as tumor necrosis factor-α (TNF-α) and interleukins.
- ***Suppress*** **leukocytes** and **macrophages** ***migration***.
- ***Stabilizing*** **mast cell** and **basophil** ***membranes*** → ↓ **Histamine** ***release***.
- ***Decrease*** **capillary permeability** → ↓ ***inflammatory*** **edema**.

Anti-allergic Effect

- ***Decrease*** **antibody** ***formation***.
- ***Decrease*** **antibody/antigen** ***reactions***.
- ***Decrease*** **tissue response** to **allergic** ***mediators***.
- **Mast cell** and **basophil** ***stabilization*** → ↓ **Histamine** ***release***.

Immunosuppressant Effect

- ***Inhibit*** **functions** of **Macrophages** and *other* **antigen-presenting cells**;
  - Inhibits production of Interleukin-12, Interferon-γ and Tumor Necrosis Factor-α (TNF-α) by antigen-presenting cells (dendritic cells, macrophages and B-lymphocytes) and T helper-1 cells.
- ***Prevents*** **T-cells proliferation**;
  - Decrease T-cells response to Interleukin-1 → T-cells unable to produce Interleukin-2.

Anti-shock Effect

- ***Unfavourable*** **stress**; such as **acute trauma, major surgery, severe infection** or **emotional stress**; ↑ **CRH** → ↑ **ACTH** → ↑ **Cortisol**;
  - **Hypervolemia** and **Hyperglycemia** ***effects***.
  - ***Potentiate*** **sympathetic action**.

Withdrawal Effect

- **Glucocorticoids** ***cannot*** *be* ***stopped*** **abruptly** and ***must*** *be* ***stopped*** **gradually** to ***avoid*** **Cortisol** ***deficiency*** *resulting from* **hypothalamic-pituitary-adrenal axis (HPA)** ***suppression*** (**Adrenal** ***Insufficiency***).
- ***Long term*** **use** ***high doses*** of **Glucocorticoids**; ***suppress*** **pituitary release** of **ACTH**, **Growth Hormone (GH)**, **Thyroid-stimulating Hormone (TSH)** and **Luteinizing Hormone (LH)**.

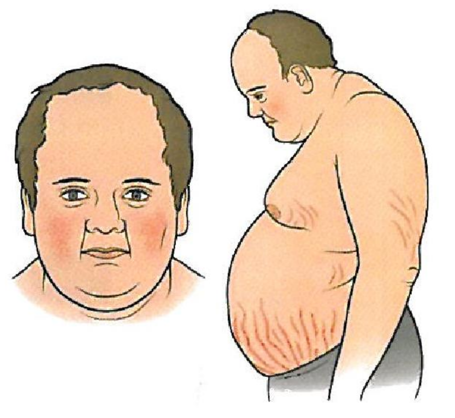
Therapeutic Uses

- **Replacement *Therapy*** for;
  - ***Primary*** **(Cortisol *deficiency*) adrenocortical insufficiency (Addison's disease)**; *see next.*
  - ***Secondary*** **(ACTH *deficiency*)** or ***tertiary*** **(CRH *deficiency*) adrenocortical insufficiency.**
  - **Congenital Adrenal Hyperplasia (CAH)**; ***congenital* mutations** of **genes** for **enzyme *mediating*** the **synthesis** of **one** or **more** of the **adrenal steroid hormones.**
- ***Diagnosis*** of **Cushing's syndrome**; **Dexamethasone *suppression* test**;
  - **Dexamethasone *suppresses* Cortisol *release*** in ***normal* individuals**, ***but*** not those with **Cushing's syndrome.**
- **Anti-inflammatory/Immunosuppressive *Therapy***; *such as* **rheumatoid arthritis, asthma exacerbations, inflammatory skin conditions, active inflammatory bowel disease, *acute* flare** of **gout** and **osteoarthritis** and ***prevent*** **rejection** in **organ transplantation.**
- ***Treatment*** of **Allergic Reactions**; *such as* **allergic rhinitis, asthma, dermatitis** and **urticaria.**
- ***Accelerate*** of **Fetal Lung Maturation (Antenatal Steroid)**; When **delivery** is ***anticipated*** ***before*** **34 weeks** of ***gestation***;
  - **IM Betamethasone 12 mg 2 doses** *given* **24 hours** ***apart*** OR
    IM Dexamethasone 6 mg 4 doses *given* **12 hours apart.**
  - **Betamethasone** is ***preferred*** *but* the recommended formulation for preterm birth is a ***less*** **available** (mixture of long-acting betamethasone acetate and fast acting betamethasone phosphate; Celestone® Soluspan®).
  - **Optimal benefit *begins* 24 hours** after initiation of therapy and ***lasts* 7 days.**
- **Cancer *Therapy* (Prednisone)**; *such as* **Acute Lymphocytic Leukemia** and ***both*** **Hodgkin** and **non-Hodgkin Lymphomas**, **Multiple Myeloma** and ***other*** **Blood Cancers.**
  - **Prednisone** also **helps** to ***decrease*** **nausea** as well as ***promote*** an **appetite.**
- **Nausea** and **vomiting**; A ***large dose*** of **Dexamethasone *reduces*** **emetic effects** of **chemotherapy** and **general anesthesia.**
- **N.B.**; - ***Short-term*** use of **Glucocorticoids**, can ***potentiate*** **renal responsiveness** to **diuretic therapy** in patients with **heart failure.**
  - **Glucocorticoids** is ***symptomatically*** **effective** in ***malignant*** **exophthalmos**, ***subacute*** **thyroiditis.**

Side Effects

Cushing's Syndrome

- **Hypothalamic–pituitary-adrenal axis *suppression*.**
- ***Inhibition*** of **leukocyte** and **monocyte** *function.*
- **Skeletal muscle *myopathy*.**
- **Aseptic necrosis** of **bone.**
- **Osteoporosis/fractures.**
- **Pseudotumor cerebri.**
- **Sodium** and **water retention.**
- **Hypokalemia/hyperglycemia.**
- **Hypertension.**
- ***Impaired*** **wound healing.**
- **Posterior subcapsular cataracts.**
- **Glaucoma.**
- **Central redistribution** of **fat.**
- **Moon facies** and **buffalo hump.**
- **Skin striae.**
- **Pancreatitis.**
- **Psychiatric disturbances.**
- **Growth *retardation*.**



Moon Facie - Buffalo Hump - Skin Striae

Patient Counselling

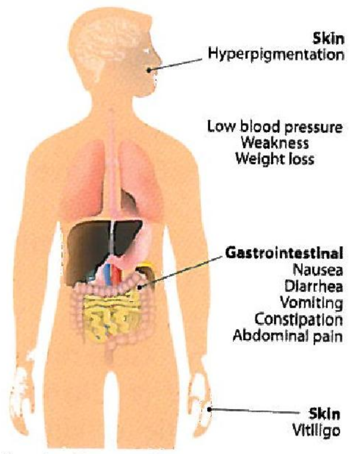
1) **Sudden withdrawal** *should be* **avoided.**
2) **Corticosteroids regimen** ***should be gradually*** **decreased.**
3) *Consider* **use** ***dosing*** *during* the **maximal adrenal cortex activity** *time*, to ***avoid*** **suppress** ***endogenous*** **corticosteroids** ***secretions***; the **BEST TIME** *between* **6-8 AM.**
4) ***Intake of*** **high protein diet** to *prevent* **muscle wasting.**
5) ***Intake of*** **high Calcium** ***supplementation*** to *prevent* **osteoporosis.**
6) ***Intake of*** **high vitamin B & vitamin D** ***supplementation*** due to deficiency by long therapy.
7) ***Intake of*** *fresh* **orange, banana juice** or **K^+** ***supplementation*** or **oral rehydration therapy** to *correct* **hypokalemia.**
8) ***Protect*** **stomach** by ***using*** **corticosteroids** ***after*** **meal** or ***using*** **H_2 blockers** or **PPIs.**
9) **MONITORING**; ***signs for*** **infection, blood pressure, blood glucose, growth** (length) *in children* and **weight.**

Disturbance of Adrenocortical Hormones Function

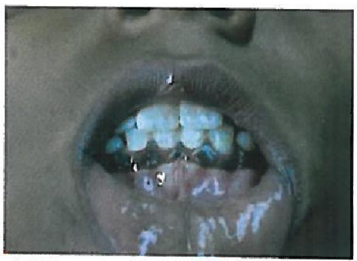
Hyposecretion of Adrenocortical Hormones [Adrenal Insufficiency]

- ***Primary*** **Adrenal Insufficiency (Addison's Disease)**; ***Damage*** to **adrenal cortex** causes ***deficiencies primarily*** in **Cortisol** and **Aldosterone** (**hypocortisolism** and **Hypoaldosteronism**);
  - *Causes*;
    - **Autoimmune disease** (**Addison's disease**); about 80% of cases.
    - **Idiopathic**; unknown cause.
    - **Congenital Adrenal Hyperplasia** (*Impaired* **steroidogenesis**),
    - **Adenoma** (**tumor**) of the **adrenal gland.**

Addison's disease



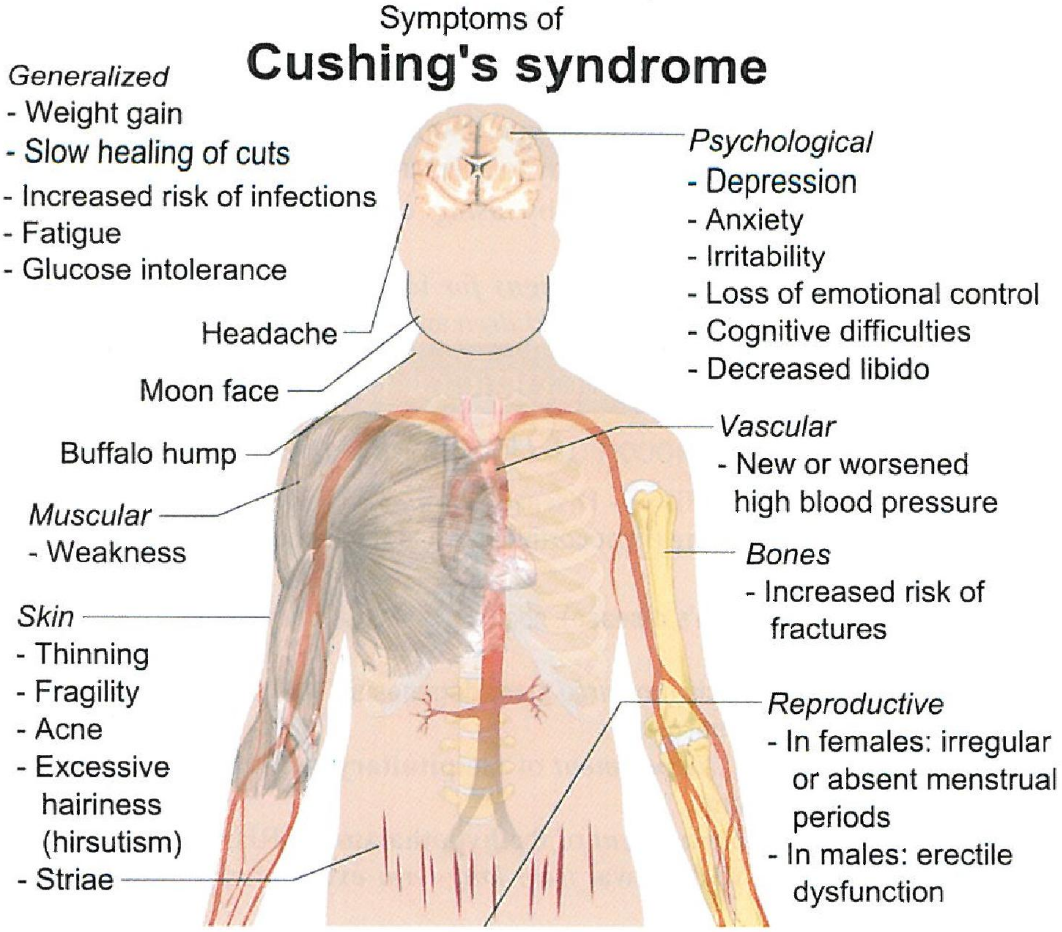
- ***Secondary*** **Adrenal Insufficiency**; ***impairment*** of the **pituitary ACTH**, ***commonly*** *due to* **pituitary adenoma.**
- ***Tertiary*** **Adrenal Insufficiency**; ***impairment*** of the **hypothalamic CRH**; *due to* **brain tumors** or ***sudden*** **withdrawal** *from* ***long-term*** **exogenous steroid** *use*.
- *Symptoms*;
  - ***General*** **symptoms**; **Weakness, GI symptoms**, *craving* for **salt, headaches, memory** *impairment*, **depression** and **postural dizziness.**
  - **Symptoms** ***more specific*** to **Addison disease**; **Weight loss, dehydration, hyponatremia, hyperkalemia,** ***elevated*** **blood urea nitrogen** and **darkening** (**hyperpigmentation**).
    - Hyperpigmentation due to melanocyte-stimulating hormone (MSH) overproduced; ACTH share the same precursor molecule, proopiomelanocortin (POMC).
    - Addison's disease is associated with the development of other autoimmune diseases, such as type I diabetes, thyroid disease (Hashimoto's thyroiditis), celiac disease or vitiligo.


Addison's hyperpigmentation

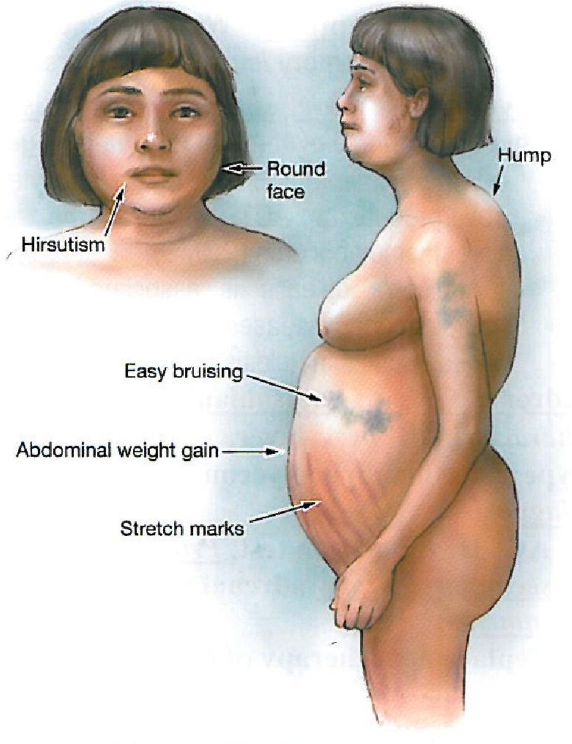
- **Adrenal Crisis** (**Addisonian Crisis**) is a ***life-threatening*** **condition** ***characterized by***; **fever, syncope, convulsion, hyperkalemia, hypercalcemia, hypoglycemia, hyponatremia** and **dehydration.**
- *Diagnosis*;
  - **ACTH stimulation test**; ***Primary*** **adrenal insufficiency** ***cannot*** be ***stimulated*** by **ACTH** where a ***secondary/tertiary*** **adrenal insufficiency** will ***respond*** to ***adequate*** **stimulation** with **ACTH.**
- *Treatments*;
  - **Replacement therapy** of ***both*** **Glucocorticoids** and **Mineralocorticoids.**
    - **Glucocorticoid** *loss*; ***Preferred*** treatment is **Hydrocortisone** (low potency and shorter half-life), **Prednisone, Dexamethasone**, or ***other*** **glucocorticoids** may be **used.**
    - **Mineralocorticoid** *loss*; **Fludrocortisone.**

Hypercortisolism (Cushing's Disease)

- **Cushing's disease**; is a ***hypersecretion*** of **Adrenocorticotropic Hormone (ACTH)** from the ***anterior*** **pituitary** (***secondary*** **hypercortisolism**) or *less* **commonly** *due to* ***hypersecretion*** of **hypothalamic Corticotropin Releasing Hormone (CRH)** (***tertiary*** **hypercortisolism**).
- **Cushing's syndrome** is a ***collection*** of **signs** and **symptoms** ***associated with excess*** **Cortisol** in the ***body*** **commonly** *due to* ***prolonged*** **exposure** to ***exogenously*** **administered corticosteroids.**


Symptoms of
Cushing's syndrome
Generalized
- Weight gain
- Slow healing of cuts
- Increased risk of infections
- Fatigue
- Glucose intolerance
Headache
Moon face
Buffalo hump
Muscular
- Weakness
Skin
- Thinning
- Fragility
- Acne
- Excessive hairiness (hirsutism)
- Striae
Psychological
- Depression
- Anxiety
- Irritability
- Loss of emotional control
- Cognitive difficulties
- Decreased libido
Vascular
- New or worsened high blood pressure
Bones
- Increased risk of fractures
Reproductive
- In females: irregular or absent menstrual periods
- In males: erectile dysfunction

- **Primary Generalized Glucocorticoid Resistance** or **Chrousos Syndrome**; is a ***rare*** **genetic** condition ***characterized*** by **end-organ** ***insensitivity*** to **glucocorticoids** (mutations of NR3C1 gene);
  - Increased production of ACTH leads to high circulating levels of Cortisol, Corticosterone and Deoxycorticosterone with mineralocorticoid activity, as well as of adrenal androgens; result in hypertension and hyperandrogenism.
- **Cushing's *Diagnosis*; Dexamethasone *suppression* test**;
  - A low dose of Dexamethasone suppresses cortisol in individuals with no pathology in endogenous cortisol production.
  - A high dose of Dexamethasone exerts negative feedback on pituitary neoplastic ACTH-producing cells (Cushing's disease), but not on ectopic ACTH-producing cells or adrenal adenoma (Cushing's syndrome).


Round face
Hirsutism
Hump
Easy bruising
Abdominal weight gain
Stretch marks

- ***Pharmacotherapy***; **Glucocorticoid Synthesis Inhibitors** and **Glucocorticoid Antagonists.**

Glucocorticoid Synthesis Inhibitors & Glucocorticoid Antagonists

Aminoglutethimide (Cytadren®)

- **Aminoglutethimide** [ah-mee-no-glue-TEH-tha-mide] is an **anti-steroid drug** act by ***block*** the ***conversion*** of **Cholesterol** *to* **Pregnenolone**; ***reduction*** in the **synthesis** of ***all*** **hormonally** ***active*** **steroids**.
- **Aminoglutethimide** also ***inhibits*** **aromatase enzyme** which is ***essential for*** the **generation** of **Estrogens** from **Androstenedione** and **Testosterone**.
- It is ***used*** for **Cushing's syndrome** and **metastatic breast cancer**.
- It has been ***off-label*** **used** by **bodybuilders** (*prevent* **muscle loss** due to **catabolism** and ***suppress*** **estrogen**).
- ***Side effects***; **skin rash**, **hepatotoxicity** and **hypothyroidism**.

Ketoconazole (Nizoral®)

- **Ketoconazole** [kee-toe-KOE-na-zole] is an **antifungal** ***imidazole*** **derivative**.
- It is a **potent** ***non-selective*** **inhibitor** of **adrenal** and **gonadal steroid** ***synthesis***.
- It ***inhibits*** the **activity** of ***several*** **enzymes** necessary for the ***conversion*** of **Cholesterol** to **steroid hormones**.
- It is ***used*** for **Cushing's syndrome** (200-1200 mg/day orally) due to ***hepatotoxicity*** **dose** ***should be*** **started** ***slowly*** (200 mg) and **increased** ***gradually*** (200 mg/d every 2–3 days up to a total daily dose of 1000 mg).

Etomidate (Amidate®)

- **Etomidate** [e-TOM-i-date] is a ***short-acting*** **IV anaesthetic** ***agent used*** for the ***induction*** of **general anaesthesia** and **sedation**.
- At ***subhypnotic*** **doses** (0.1 mg/kg per hour) **Etomidate** ***inhibits*** **adrenal steroidogenesis**.
- It is the ***only*** **parenteral** medication available in the ***treatment*** of ***severe*** **Cushing's syndrome**.

Metyrapone (Metopirone®)

- **Metyrapone** [me-TEER-a-pone] is a ***reversibly inhibiting*** **steroid 11β-hydroxylase**, this ***stimulates*** **ACTH** ***secretion***, which in turn ***increases*** plasma **11-deoxycortisol** ***levels***.
- ***Uses***;
  - ***Diagnosis*** of **adrenal insufficiency** (by measure plasma level ACTH and 11-deoxycortisol).
  - **Cushing's syndrome**.

Trilostane (Vetoryl®)

- **Trilostane** is a ***steroidogenesis inhibitor*** (3β-17 hydroxysteroid dehydrogenase inhibitor) which is ***used*** in the treatment of **Cushing's syndrome**. It was withdrawn from human use in the United States.

Abiraterone (Zytiga®)

- **Abiraterone** [A-bir-A-te-rone] is an ***antiandrogen agent*** used in the **treatment** of **prostate cancer**.
- It ***blocks*** **17α-hydroxylase** (P450c17) and **17,20-lyase**, and *predictably* ***reduces synthesis*** of **Cortisol** in the **adrenal** and **Gonadal Steroids** in the **gonads**.

Mifepristone (Mifeprex®)

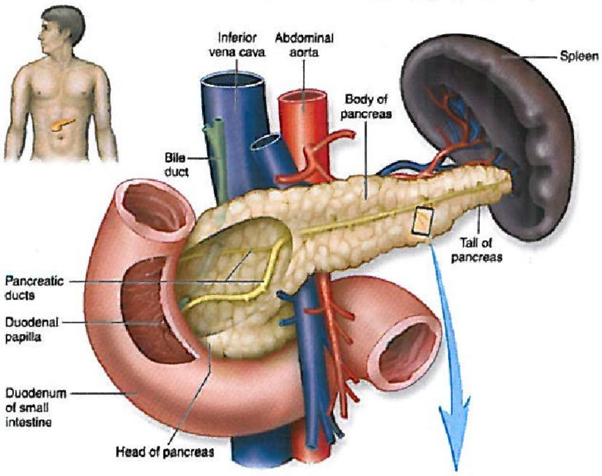
- **Mifepristone** [mi-FE-pris-tone] is an ***antiprogestogen***, as *well as* an ***antiglucocorticoid*** and ***antiandrogen*** to a *much* ***lesser*** **extent**.
- **Mifepristone** is **abortifacient drug** used in ***combination*** with **Misoprostol** in **abortion**.
- **Mifepristone** is used to ***control*** **hyperglycemia** (secondary to hypercortisolism) in patients with ***endogenous*** **Cushing's syndrome** who have **type 2 diabetes mellitus** or **glucose intolerance** and who **failed surgery** or who are ***not*** **surgical candidates**.
- **Mifepristone** is also used for **emergency contraception** (taken after sexual intercourse).

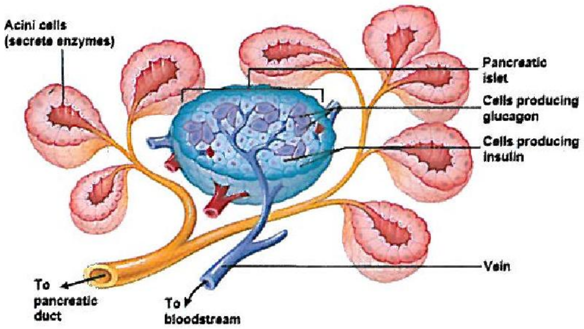
Mitotane (Lysodren®)

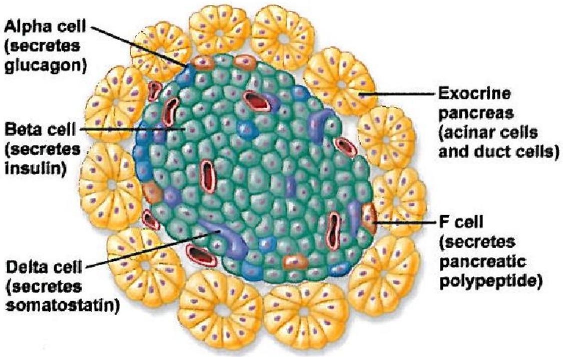
- **Mitotane** [MYE-toe-tane] is a ***steroidogenesis inhibitor*** and ***cytostatic drug***, is **used** in the treatment of **adrenocortical carcinoma** and **Cushing's syndrome**.
- **Mitotane** is ***related to*** the **DDT** (**dichlorodiphenyltrichloroethane**) *class of* **insecticides**, has a ***nonselective*** **cytotoxic action** on the **adrenal cortex**.

Pancreatic Hormones

- The **pancreas** is a ***glandular*** **organ** in the **digestive system** and **endocrine system**.
- The **pancreas** is ***producing*** *several* **important hormones** ***control*** **blood sugar** and **metabolism** within the body, and also in the ***secretion*** of **substances** (**pancreatic juice**) which ***help*** **digestion**.
- **Hormones** (**Endocrine System**);
  - * **Insulin** and **Glucagon**; control blood sugar.
  - * **Somatostatin**; inhibits the release of growth hormone, *TSH, GI hormones and pancreatic hormones.*
  - * **Pancreatic Polypeptide**; regulate pancreatic secretion and gastric emptying.
- **Pancreatic Juice** (**Digestive System**);
  - * **Bicarbonate**; neutralize acidity.
  - * **Trypsinogen** (**Trypsin** *precursor*); break down proteins.
  - * **Chymotrypsinogen** (**Chymotrypsin**); break proteins.
  - * **Elastase**; break down proteins.
  - * **Carboxypeptidase**; break down proteins.
  - * **Nucleases**; break down nucleic acids.
  - * **Lipase**; break down lipids.
  - * **Amylase**; break down carbohydrates.
- **Pancreatic Tissues**;
  - A) **Pancreatic acini**;
    - **Exocrine** *part* (*About* **80%** of the **pancreas volume**)
    - ***Secrete*** **pancreatic juice** ***into*** the **duodenum**.
  - B) **Pancreatic islets** or **islets** *of* **Langerhans**;
    - **Endocrine** *part* (**1-2%** of the **pancreas volume**).
    - **Alpha** (α) **cells** (20% of total islet cells); **Glucagon**.
    - **Beta** (β) **cells** (≈70%); **Insulin** & **Amylin** (100:1).
    - **Delta** (δ) **cells** (<10%); **Somatostatin**.
    - **PP** (γ or **F**) **cells**; (<5%); **Pancreatic Polypeptide**.
    - **Epsilon cells** (<1%); **Ghrelin**.
      - **Ghrelin** (**hunger hormone**); produced by **GIT** and ***regulate*** **appetite** in **CNS** by ***inducing*** **hunger**.
      - **Leptin**; *produced by* **adipose cells** & ***regulate*** **energy balance** by ***inhibiting*** **hunger** (***opposite*** to **Ghrelin**)


Inferior vena cava
Abdominal aorta
Spleen
Body of pancreas
Bile duct
Tail of pancreas
Pancreatic ducts
Duodenal papilla
Duodenum of small intestine
Head of pancreas


Acini cells (secrete enzymes)
Pancreatic islet
Cells producing glucagon
Cells producing insulin
Vein
To pancreatic duct
To bloodstream


Alpha cell (secretes glucagon)
Beta cell (secretes insulin)
Delta cell (secretes somatostatin)
Exocrine pancreas (acinar cells and duct cells)
F cell (secretes pancreatic polypeptide)

Glucagon

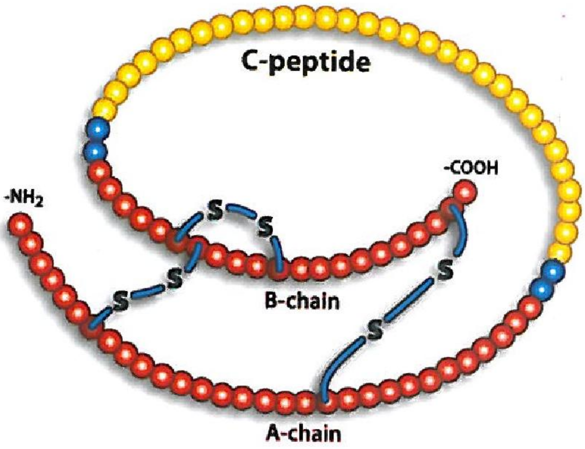
- **Glucagon** effect is ***opposite to*** that of **Insulin**, which ***lowers*** the ***extracellular*** **Glucose**.
- **Glucagon** ***acting*** *through* **G protein-coupled receptors** (*via* **cAMP**) in **heart**, **smooth muscle** and **liver**.
- ***Function***; ***increases*** **heart rate** and **force of contraction**, ***increases*** **hepatic glycogenolysis** and **gluconeogenesis**, and ***relaxes*** **smooth muscle** *particularly* in the **gut**.
- ***Uses***; It is **used IM** or **IV** to ***treat*** **severe hypoglycemia** (**Hypoglycemia Antidotes**), **β-blocker** and **calcium channel blocker toxicity** (increases cardiac cAMP without requiring access to β receptors), and **GI Radiography** (decrease GI motility).

Amylin

- **Amylin** is a ***synergistic*** **partner** to **Insulin**, it ***regulate*** **blood glucose** by ***slowing*** **gastric emptying**, **promoting satiety** (via hypothalamic receptors), and ***inhibiting*** **inappropriate** ***secretion*** of **Glucagon**.
- **Pramlintide** (Symlin®) is an ***injectable*** **amylin analogue** drug for **diabetes** (both **type 1** and **2**).

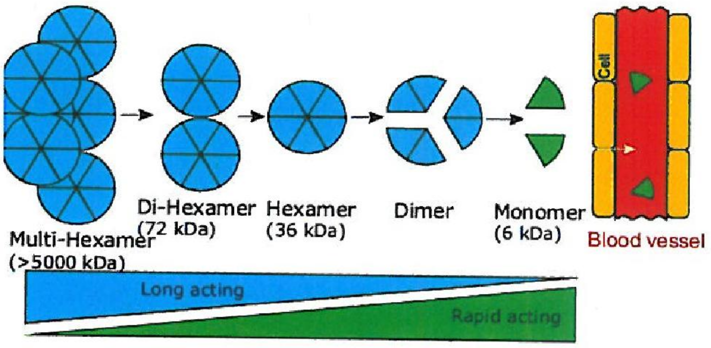
Insulin

- **Insulin** is a **peptide hormone** *produced by* **β-cells** of the **pancreatic islets**, and it is *considered to be* the ***main* anabolic hormone** of the **body**.
- **Insulin** word is *derived from* **Latin word "insula"** *means* **island (pancreatic islets)**.
- **Insulin** is ***synthesized as*** the **prohormone Proinsulin**, an **86-amino-acid** ***single-chain*** **polypeptide**.
- **Proinsulin = Insulin (A + B chain; 51 amino acids) + C peptide (31 amino acids)**.
- **Insulin** is a ***dimer of*** **51 amino acids**; an **A-chain** and a **B-chain**, which are ***linked together*** by **disulfide bonds**.



- **C-peptide** has ***no influence*** on **Glucose** or **Lipid *metabolism***, *but* have **beneficial *effects*** on **peripheral nerves**, **kidneys**, and **brain** (***protection*** *from* **diabetes complications**; **retinopathy**, **nephropathy** and **neuropathy**).
- **C-peptide *binds*** to **cell membranes**, ***resulting*** in ***stimulation*** of ***endothelial*** **nitric oxide synthase** (**eNOS**) and **Na$^+$/K$^+$-ATPase**.
- ***Measuring*** **C-peptide** can ***help*** to **monitor Insulin *production*** in the **body** (**C-peptide Test**);
  - **C-peptide levels** are ***increased*** in:
    - Insulinoma (tumor of the pancreas).
    - Sulfonylurea intoxication.
    - Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS).
    - Insulin resistance state (e.g., obesity, Cushing and polycystic ovary).
    - Chronic kidney disease.
  - **C-peptide levels** are ***decreased*** in:
    - Type 1 diabetes mellitus.
    - Exogenous insulin injection.
    - Hypoglycemia due to insulin-like growth factor secreting tumor.
    - Insulin-independent hypoglycemia.

- **Insulin** is **storage** in **granules *within*** the **β-cells** as ***insoluble*** **crystalline Hexameric-Insulin**;
  - **Zn^{2+}** is ***essential*** for **storage** of **Insulin**.
  - **2 Zn^{2+} ions *coordinate* 6 Insulin *monomers*** to ***form*** the **hexameric-Insulin** on which ***maturated* Insulin crystals** are based.
  - The **hexamer** is an ***inactive*** form with **long-term stability**, however, the **monomer** is a *much* **faster-reacting drug** because diffusion rate is inversely related to particle size.

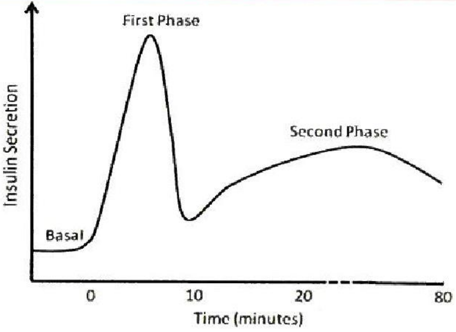


Normal Values

***- Reference Range* of Insulin *Levels*; Medscape**

Fasting	< 25 mIU/L
30 minutes after glucose administration	30-230 mIU/L
1 hour after glucose administration	18-276 mIU/L
2 hour after glucose administration	16-166 mIU/L
≥3 hours after glucose administration	< 25 mIU/L

Insulin Release

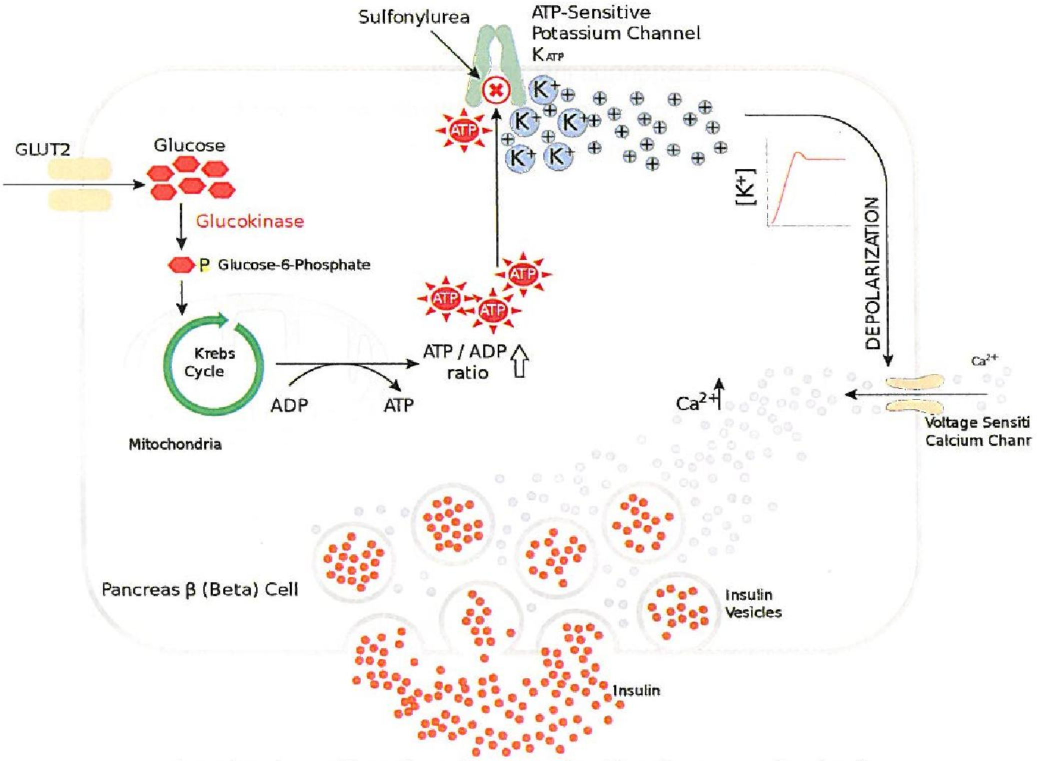


A) **Phases** of **Release**;

- **First-phase** (**rapid**/**bolus**); ***Rapidly*** **triggered** in *response to* ***increased*** **blood glucose levels**, **begins** ***within*** **2 minutes** of **nutrient** ***ingestion*** and ***lasts*** *about* **10 minutes**.
- **Second-phase** (**sustained**/**intermediate**); ***Sustained until*** **normoglycemia** is ***restored***, **peaking** in **2-3 hours**.
- **β-cells** ***secrete*** **Insulin** *over* **50%** of ***total*** **24 hour** *during* **fasting** (**basal**) **state**.
  - **Basal** ***secretion***; ***Continuous*** **release** of **insulin**.
  - **Bolus** **secretion**; **Insulin** ***released*** **in response** to an ***increase*** in **blood sugar**.

B) **Mechanism** of **Release**;

- The **β-cells** ***respond*** to ***many*** **nutrients** in the **blood circulation**, *including* **Glucose**, other **monosaccharides**, **amino acids** and **fatty acids**.
- **Glucose** is the ***primary*** **stimuli** for **Insulin** ***release***.
- **Glucose** ***enters*** the **β-cells** through the **glucose transporters**, **GLUT2** *via* **facilitated diffusion**.
- **Glucose** is ***phosphorylated*** to **glucose-6-phosphate** (**G-6-P**) by **glucokinase** (**hexokinase IV**).
- **Glucose-6-phosphate** ***enters*** **glycolytic pathway** (***glycolysis***) and then, via the **pyruvate dehydrogenase** ***reaction***, into the **Krebs cycle**, where ***multiple***, ***high-energy*** **ATP molecules** are ***produced by*** the **oxidation** of **acetyl CoA** (Krebs cycle substrate), *leading to* a ***rise*** in the **ATP**:**ADP ratio** ***within*** the **cell**.
- An ***increased*** **intracellular** **ATP**:**ADP ratio** ***closes*** the **ATP-sensitive potassium channel**. This ***prevents*** K^+ from ***leaving*** the **cell**, *leading to* a ***buildup*** of ***intracellular*** K^+, *leading to* **depolarization** of the **cell surface** ***membrane***.
- *Upon* **depolarization**, **voltage-gated calcium channels** ***open***, allowing Ca^{2+} to **move** ***into*** the **cell** *by* **facilitated diffusion**.
- An ***increased*** **intracellular** Ca^{2+} *leading to* ***increased*** Ca^{2+} ***release*** from **endoplasmic reticulum**, ***raises*** the **cytosolic** ***concentration*** of Ca^{2+} *leading to* ***increase*** **Insulin** ***secretion*** into the **blood** *via* **exocytosis**.


Sulfonylurea
ATP-Sensitive Potassium Channel K_ATP
K+
ATP
GLUT2
Glucose
Glucokinase
P Glucose-6-Phosphate
Krebs Cycle
Mitochondria
ADP
ATP
ATP / ADP ratio
[K+]
DEPOLARIZATION
Ca2+
Voltage Sensiti Calcium Chanr
Pancreas β (Beta) Cell
Insulin Vesicles
Insulin

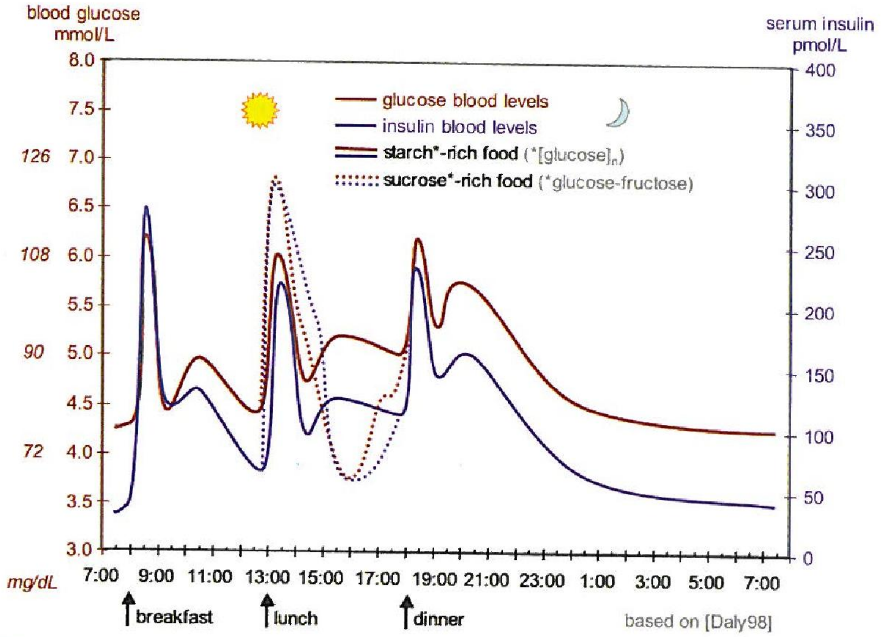
(mechanism of insulin release and sulfonylurea mechanism)

- The ***half-life*** of ***circulating*** **Insulin** is **3–5 minutes** (***rapidly*** **cleared** *by* **liver** and **kidney**).

Regulation

Blood Glucose

- **Glucose** is the ***primary*** **stimuli** for **Insulin** *release*.
- ↑ *blood* **Glucose** *level* → ↑ **Insulin** *secretion*.
- **Glucose** ***does*** ***not*** **require Insulin** *action* to *enter* the **β-cell** (*due to* the **Glucose** is **transported** *across* **GLUT2**).



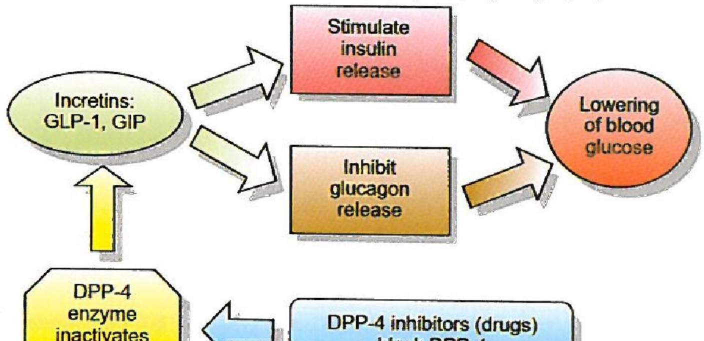
based on [Daly98]

Amino Acids

- **Amino acids** *such as* **Arginine** (cationic amino acid, which leads to membrane depolarization), **Alanine**, **Leucine** and **Glutamine** (via the Krebs cycle to generate ATP) → ↑ **Insulin** *secretion*.

Gastrointestinal Hormones

- **Glucagon-like Peptide-1 (GLP-1)** & **Gastric Inhibitory Peptide** [or Glucose-dependent Insulinotropic Peptide] **(GIP)** are **Incretins** and **released** ***after*** **eating** → ↑ **Insulin** *secretion* and
  ↓ **Glucagon** *secretion*.
- *Both* **GLP-1** & **GIP** are *rapidly* **inactivated** by **dipeptidyl peptidase-4 (DPP-4)**.


Incretins:
GLP-1, GIP
Stimulate
insulin
release
Inhibit
glucagon
release
Lowering
of blood
glucose
DPP-4
enzyme
inactivates
incretins
DPP-4 inhibitors (drugs)
block DPP-4

- **Somatostatin** → ↓ **pancreatic hormones (Insulin & Glucagon)** *release*.
- *N.B.*; **Growth Hormone (GH)**, **Prolactin** and **Glucagon** *increase* **glucose-stimulated insulin release**, *while* **GH** and **Prolactin** *increase* **insulin gene** *expression* & **β-cell proliferation**.

Autonomic Nervous System

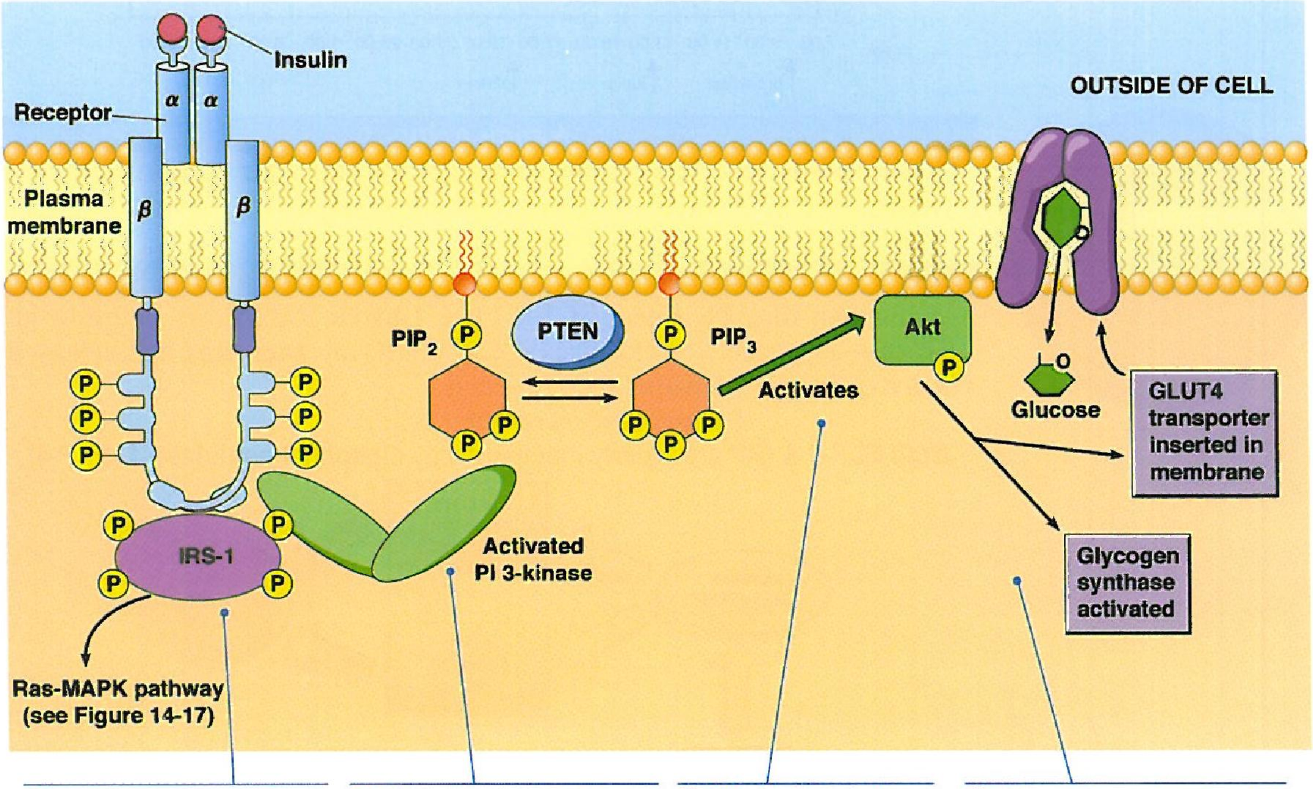
- **Sympathetic**; → ***strongly*** ↓ **Insulin** *release* (*via* **α_2 adrenergic receptors**).
  → ***minor*** ↑ **Insulin** *release* (*via* **β_2 receptors**).
- **Parasympathetic**; ↑ **Insulin** *release* (*via* **M_3 receptors** *through* **vagus nerve**).

Drugs

- **Sulfonylurea drugs** → ↑ **Insulin** *release*.

Mechanism OF Action

- The *effects* of **Insulin** are *initiated by* **its** ***binding*** to **insulin receptors** *present in* the **cell membrane.**
- **Insulin Receptor** *contains* **4 subunits**;
    - **2 α-subunits;** ***outside*** the **cell membrane.**
    - **2 β-subunits; penetrate** *through* the **membrane.**
- **Insulin** ***binds*** to the **α-subunits** → ↑ **tyrosine kinase enzyme** ***activity*** on **β-subunits** → ***phosphorylation*** **of Insulin Receptor Substrate-1(IRS-1).**
- **IRS** ***activates*** **phosphoinositol 3-kinase (PI3K).**
- **PI3K** ***converts*** **a phosphatidylinositol bisphosphate (PIP2)** in the **cell membrane** ***into*** **phosphatidylinositol triphosphate (PIP3).**
- **PIP3** ***activates*** **Akt/Protein Kinase-B (PKB)** → ***activation*** of ***other*** **kinases;** *leads to;*
    - * ***Facilitates*** the **fusion** of **GLUT4** ***with*** the **cell membrane** → ***increase*** **Glucose** ***transporters*** into **cell membranes** of **muscle** and **fat cells.**
    - * ***Increase*** **glycogen synthase** ***activity*** → ***increase*** **synthesis** of **Glycogen** in **liver** and **muscle tissue.**
    - * ***Multiple*** **effects** on **protein synthesis** and **lipogenesis.**
    - * ***Activation*** of **transcription factors** that ***enhance*** **DNA synthesis** and **cell growth** and **division.**


Insulin
Receptor
α
α
OUTSIDE OF CELL
Plasma membrane
β
β
PIP2
P
PTEN
P
PIP3
Activates
Akt
P
Glucose
GLUT4 transporter inserted in membrane
P
IRS-1
Activated PI 3-kinase
Glycogen synthase activated
Ras-MAPK pathway (see Figure 14-17)

① When the insulin receptor binds insulin, the activated receptor phosphorylates the IRS-1 protein. IRS-1 can lead to recruitment of GRB2, activating the Ras pathway.

② IRS-1 activates PI 3-kinase, which catalyzes the addition of a phosphate group to the membrane lipid PIP_2, thereby converting it to PIP_3. PTEN can convert PIP_3 back to PIP_2.

③ PIP_3 binds a protein kinase called Akt, which is activated by other protein kinases.

④ Akt catalyzes phorphorylation of key proteins, leading to an increase in glycogen synthase activity and recruitment of the glucose transporter, GLUT4, to the membrane

Glucose Transporters		
Transporter	**Tissues**	**Function**
GLUT 1	All tissues especially red cells and brain	Transport across BBB
GLUT 2	Beta cells of pancreas, liver, kidney and gut	Regulation of insulin release
GLUT 3	brain and placenta	Uptake into neurons and other tissues
GLUT 4	Muscles and adipose tissues	Insulin-mediated uptake of glucose
GLUT 5	Gut and kidney	Absorption of fructose

Function

Carbohydrate Metabolism

- *Stimulates* **glucose** ***uptake*** in **muscles** and **fat tissues**; by insertion of the GLUT4 transporter in the cell membranes.
- ***Increase*** **glycogenesis**; by Increase activity of glycogen synthase.
- ***Increase*** **glycolysis** and ***decrease*** **gluconeogenesis.**

Lipid Metabolism

[↑ Lipogenesis and ↓ Lipolysis]

- ***Stimulates*** **fatty acid** ***synthesis*** in **adipose tissue**, **liver** and **lactating mammary glands**; by increase activity of acetyl-CoA carboxylase.
- ***Stimulates*** **triglyceride** ***synthesis*** in **adipose tissue** and **liver**; by increase esterification of fatty acid with glycerol.
- ***Stimulates*** **cholesterol** ***synthesis***; by increase activity of HMG Co-A reductase.
- ***Inhibit*** **ketogenesis** (ketone bodies formation); by inhibits lipolysis.
- **Ketone bodies** are ***particularly*** **important** for the **brain** which has ***no other*** **substantial** ***non*-glucose-*derived*** **energy source**.
- **Ketone bodies** are **Acetoacetate**, **β-hydroxybutyrate** (or **3-hydroxybutyrate**) and **Acetone**.
- **Ketone bodies** are ***increase*** *during* **fasting** and ***prolonged*** **exercise**.
- **Diabetes** is the ***most*** **common pathological cause** of ***elevated*** **blood ketones**.
- **Ketone bodies** are acidic, and, if **levels** of these **ketone bodies** are ***too high***, the **pH** of the **blood** ***drops***, resulting in **ketoacidosis**.
- **Diabetic ketoacidosis** (**DKA**) is a *potentially* ***life-threatening*** **complication** of **diabetes mellitus**.

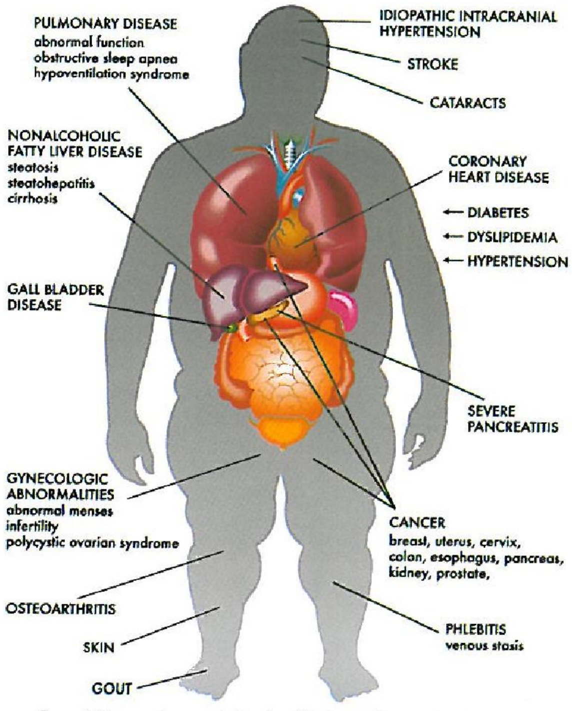
Protein Metabolism

[Anabolic]

- ***Increase*** **amino acid** ***uptake.***
- ***Promotes*** **protein synthesis** and ***decrease*** **proteolysis** (protein breakdown).
- N.B.; - Insulin can bind to the receptors for IGF-1 but with much lower affinity and IGF-1 binds weakly to the insulin receptor.
  - Insulin-like growth factors (IGF) are so-called because they have significant structural homology with proinsulin.

Insulin Resistance

- **Insulin Resistance (IR)**; ***reduced*** **biological response** to **Insulin.**
- ***Causes***;
  - **A) Pre-receptor**;
    - ***Abnormal*** **insulin** (mutations).
    - **Anti-insulin antibodies.**
  - **B) Receptor**;
    - ***Decreased*** **number** of **receptors** (mainly, failure to activate tyrosine kinase).
    - ***Reduced*** **binding** of **insulin.**
    - **Insulin receptor** ***mutations.***
    - **Insulin receptor–*blocking*** **antibodies.**
  - **C) Post-receptor**;
    - ***Defective*** **signal transduction.**
    - ***Mutations*** of **GLUT4** (rare).
- ***Specific conditions***;
  - **Aging**; (decreased production of GLUT-4).
  - **Cushing syndrome**, **acromegaly** and **stress states**.
  - Medications; **Glucocorticoids**, **Cyclosporine**, **Niacin** and **Protease Inhibitors**.
  - ***High*** **sodium intake**; ↑ Glucocorticoid production.
  - **Insulin therapy**: Low-titer anti-insulin antibody.


PULMONARY DISEASE
abnormal function
obstructive sleep apnea
hypoventilation syndrome
IDIOPATHIC INTRACRANIAL HYPERTENSION
STROKE
CATARACTS
NONALCOHOLIC FATTY LIVER DISEASE
steatosis
steatohepatitis
cirrhosis
CORONARY HEART DISEASE
← DIABETES
← DYSLIPIDEMIA
← HYPERTENSION
GALL BLADDER DISEASE
SEVERE PANCREATITIS
GYNECOLOGIC ABNORMALITIES
abnormal menses
infertility
polycystic ovarian syndrome
CANCER
breast, uterus, cervix, colon, esophagus, pancreas, kidney, prostate,
OSTEOARTHRITIS
SKIN
PHLEBITIS
venous stasis
GOUT

Conditions Associated with Insulin Resistance

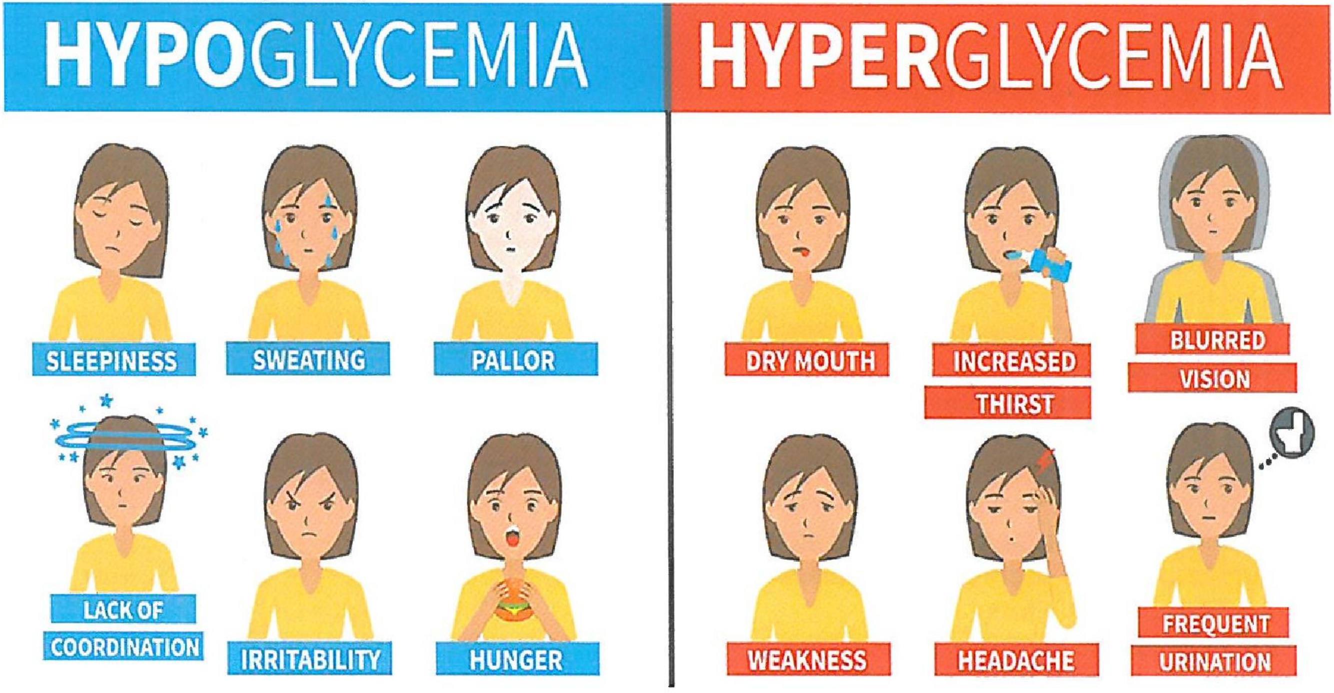
Disturbance of Insulin Hormone Functions

Hypersecretion (Hypoglycemia)

- **Hypoglycemia** is *characterized by* a ***reduction*** in **blood glucose concentration** to a **level** that may ***induce*** **symptoms** or **signs** such as ***altered*** **mental status** and/or **sympathetic nervous system *stimulation*.**
- ***Immediate*** **treatment** of **hypoglycemia** is ***necessary*** when **blood sugar levels** are at **70 mg/dL** (3.9 mmol/L) or ***below***.
- ***Symptoms***;
  - **A) Neurogenic** (adrenergic) (sympathoadrenal activation) **symptoms**;
    - **Sweating, shakiness, tachycardia, anxiety** and a **sensation** of **hunger**.
  - **B) Neuroglycopenic symptoms**:
    - **Weakness, tiredness** or **dizziness**.
    - ***Inappropriate*** **behavior** (sometimes mistaken for inebriation).
    - **Confusion, blurred vision** and in *extreme cases*, **coma** and **death**.
- ***Causes***;
  - **Anti-diabetic drugs**; such as insulin, and sulfonylureas.
  - ***Excessive*** **alcohol consumption**.
  - ***Some*** **critical illnesses**; kidney failure, tumors of the pancreas (insulinoma), liver disease, hypothyroidism, starvation, inborn errors of metabolism, severe infections and Addison's disease.
- ***Pharmacotherapy***;
  - **Glucose *supplements***; **Glucose** (**Dextrose**)
  - **Glucose-*elevating* agents**; **Glucagon**
  - ***Inhibitors*** **of insulin secretion**; **Diazoxide** or **Octreotide**
  - **Antineoplastic *agents***; **Streptozocin** (used in insulinoma).

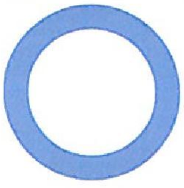
Hyposecretion (Hyperglycemia)

- **Hyperglycemia** is a ***condition*** in which an ***excessive*** **amount** of **glucose** in the **blood**.
- ***Symptoms***;
  - **Polyphagia** (frequent hunger), **Polydipsia** (frequent thirst) and **Polyuria** (increased volume of urination).
  - **Dry mouth, blurred vision, fatigue** and **weight loss**.
  - **Tingling** in **feet** and **erectile dysfunction**.
  - ***Recurrent*** **infections** and ***poor*** **wound healing**.
  - **Fruity (Acetone) smelling breath *odour*** (**Ketoacidosis**).
  - **Cardiac arrhythmia, seizures** and **coma**.


HYPOGLYCEMIA
HYPERGLYCEMIA
SLEEPINESS
SWEATING
PALLOR
DRY MOUTH
INCREASED THIRST
BLURRED VISION
LACK OF COORDINATION
IRRITABILITY
HUNGER
WEAKNESS
HEADACHE
FREQUENT URINATION

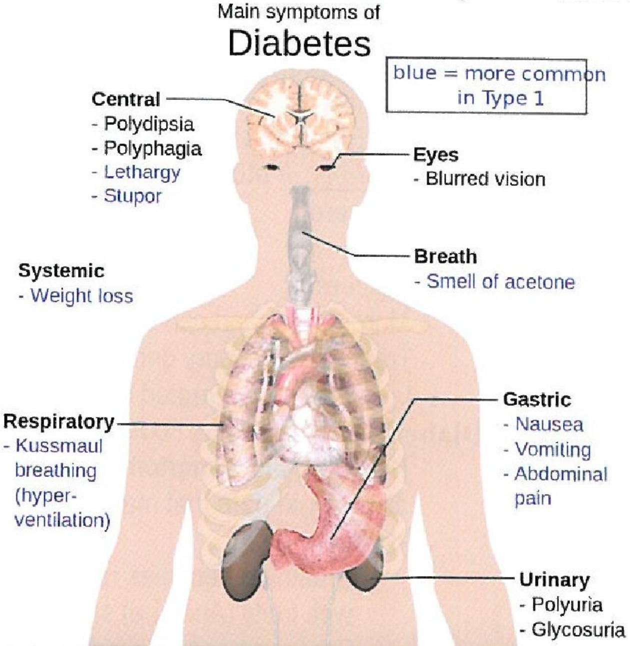
Diabetes Mellitus (DM)

- **Diabetes Mellitus** (**DM**) is a **disease state** that ***results*** in an *inappropriately* ***high*** **blood sugar levels** ***over*** a **prolonged** ***period***.
- There are **3** ***main*** **types** of **diabetes mellitus**:
  1) **Type 1 DM**; ***results from*** the **pancreas's** ***failure*** to **produce** ***enough*** **insulin**.
     - Previously referred to as; Insulin-dependent Diabetes Mellitus (IDDM).
  2) **Type 2 DM**; *begins with* **insulin resistance** (cells fail to respond to insulin properly).
     - Previously referred to as; Non-insulin-dependent diabetes mellitus (NIDDM).
  3) **Gestational diabetes**; *occurs* when **pregnant women** ***without*** a ***previous*** **history** of **diabetes** *develop* ***high*** **blood sugar** ***levels***.
     - Common during the last three months of pregnancy.
     - Pregnancy hormones and other factors are interfere with the insulin action as it binds to the insulin receptor.



universal blue circle symbol for diabetes

- ***Main Symptoms***; (* Classical Symptoms).
  - * **Polyphagia** (frequent hunger)
  - * **Polydipsia** (frequent thirst)
  - * **Polyuria** (increased volume of urination).
  - * ***Unexplained*** **weight loss**.
  - **Lethargy**.
  - **Diabetic Ketoacidosis** (**DKA**); **Fruity (Acetone)** ***smelling*** **breath odour**.



- ***Diagnosis***;

Diagnostic Criteria	Random Plasma Glucose (mg/dL)	Fasting Plasma Glucose (mg/dL)	2-Hour Post-glucose (75 g) Load (mg/dL)	Glycated Hemoglobin [A1C] (%)
Prediabetes		100–125	140–199	5.7–6.4
Diabetes	≥ 200 (with symptoms)	≥ 126	≥ 200	≥ 6.5

- **Renal Threshold** of **Glucose** (**RTG**); When the **blood glucose level** ***exceeds*** about **160–180 mg/dL**, the **proximal tubule** *becomes* ***overwhelmed*** and **begins** to ***excrete*** **glucose** in the **urine**.
- ***Causes*** and ***Risk Factors***;

	Type 1 DM [Insulin Deficiency]	**Type 2 DM** [Insulin Resistance]
Causes	- ***Autoimmune*** **destruction** of **insulin-producing beta cells** of **pancreas**. - ***Most common*** **type** in **children**.	- ***Defective*** **responsiveness** of **body tissues** to **insulin**. - ***Common*** **type** in **adult**.
Risk factors	1) **Genetics**; > 50 genes are associated. 2) **Dietary factors**; - ***Low*** **vitamin D** ***consumption***. - ***Early*** **exposure** (infancy) to **cow's milk** 3) **Viral infection**; such as enterovirus infections, mumps and rubella. 4) **Cytotoxic drugs** and **chemicals**; - **Pyrinuron**; *rodenticide* - **Streptozocin**; *antineoplastic*. 5) **Geography**; European populations, with people from northern Europe more often affected than those from Mediterranean regions and least prevalent in East Asians.	1) **Family history** ***of*** **type 2 DM**. 2) **Age** ***greater than*** **45 years**; risk increases in older; testing should be done. 3) ***Over*** **Weight**; greater than 120% of desirable body weight; more fatty tissue more resistant to insulin. 4) **Polycystic Ovarian Syndrome**; which results in insulin resistance. 5) ***History*** of **gestational diabetes**. 6) **Hypertension** or **dyslipidemia** 7) **Inactivity**; *leads to* impaired glucose control 8) **Race**; Hispanic, Native American, African American, Asian American, or Pacific Islander descent.

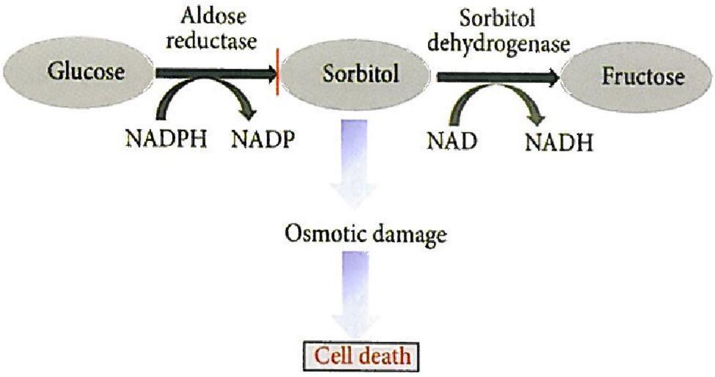
- Vitamin D *deficiency* are *linked to* Type 1 DM in *children*, Type 2 DM and Gestational Diabetes.

- ***Screening***;
  - **A) American Diabetes Association (ADA) recommendations** for *screening*;
    - **Children** who are **overweight** PLUS have **two** of the ***following***:
      - Family history of type 2 DM
      - Native American, African American, Latino, Asian American, or Pacific Islander.
      - Has signs of insulin resistance or conditions associated with insulin resistance.
      - Maternal history of diabetes or gestational diabetes during child's gestation.
    - **Screening *should* occur** at **3-year intervals *beginning*** when the **child** is **10 years** of **age** or at the ***onset*** of **puberty**, whichever comes first.
  - **B) *Additional* recommendations**;
    - Asian children, regardless of BMI, with either a history of abnormally low or high birth weight and a family history of diabetes.
    - Children with a BMI at the 95th percentile or higher, regardless of family history or associated features.
- ***Diabetic Complications***; *If* **blood sugar levels *well*-controlled**, the **complications** of **diabetes** are ***far less* common** and ***less* severe**.
  - **Acute Complications**;
    - **Hypoglycemia**;
      - More severe and can cause brain damage and death.
      - Treated with sugary drinks as soon possible and IV infusion of dextrose.
      - In severe cases treated with IV glucagon.
    - **Diabetic Ketoacidosis (DKA)**;
      - **Predominant symptoms**; **nausea** and **vomiting**, **thirst**, ***excessive* urine production** and **abdominal pain** that may be ***severe***.
      - In ***severe* DKA**;
        - Breathing becomes rapid and of a deep, gasping character, called "Kussmaul breathing" with fruity (Acetone) smelling breath odour.
        - Confusion or a marked decrease in alertness, including coma.
        - The primary treatment of DKA is with IV fluids and insulin (IV or SC depending on severity), sodium bicarbonate may be given.
        - Death can result from inadequate or delayed treatment, or from complications (e.g., brain edema especially in children).
    - **Hyperglycemia Hyperosmolar State (HHS)**;
      - HHS is characterized by hyperglycemia, hyperosmolarity and dehydration without significant ketoacidosis.
      - Hyperglycemia → glucosuria (renal threshold; >180 mg/dL) → loss of more water than sodium (excessive urination; osmotic diuresis) leads to → hyperosmolarity → dehydration → weakness, legs cramps, trouble seeing, risk of blood clotting (hyperviscosity), and an altered level of consciousness or coma.
      - The primary treatment of HHS is IV fluids and insulin; potassium replacement and heparin (decrease the risk of blood clotting) may be given.
    - **Diabetic Coma**; Severe hypoglycemia, DKA and HHS.
  - **Chronic complications**;
    - **Microangiopathy**;
      - ***Diabetic* Nephropathy**; damage to the kidney which can lead to chronic renal failure.
      - ***Diabetic* Neuropathy**; abnormal and decreased sensation, starting with the feet but potentially in other nerves, later often fingers and hands.
      - ***Diabetic* Retinopathy**; damage to the small blood vessels and neurons of the retina and may develop macular edema (swelling of the macula), which can lead to severe vision loss or blindness.
      - ***Others***; diabetic cardiomyopathy and encephalopathy, erectile dysfunction and Periodontal disease (gum disease).
    - **Macrovascular Disease**; **Coronary artery disease**, **peripheral vascular disease**, **diabetic foot** and **female infertility**.
    - **Immune Dysfunction**; Infections & autoimmune diseases such as leukocytoclastic vasculitis (LCV).

- ***Common* Hypothesis** in **Pathophysiology** of **Diabetic Complications**;

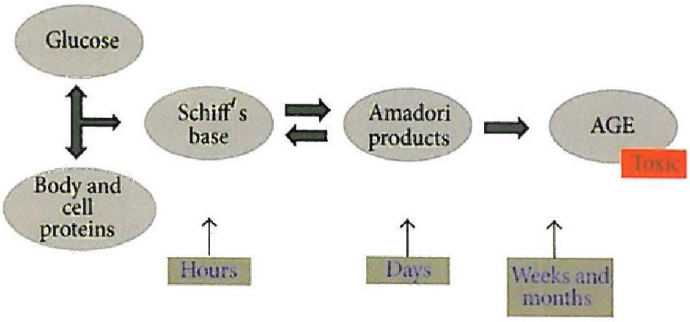
A) Polyol pathway;

- ***Chronic* hyperglycemia**; **Glucose** is ***reduced to* Sorbitol**, which is then ***converted to* Fructose**.
- ***Increase* in intracellular Sorbitol *levels* → *accumulates*** and causes **osmotic *damage***.
- **Polyol pathway *increases*** in **activity** in **tissues *like* retina, kidney, peripheral nerves**, and **blood vessels** where **Insulin** is ***not required*** for **cellular Glucose *uptake*** (***NOT*** **GLUT 4**).


Aldose reductase
Glucose
Sorbitol
Sorbitol dehydrogenase
Fructose
NADPH
NADP
NAD
NADH
Osmotic damage
Cell death

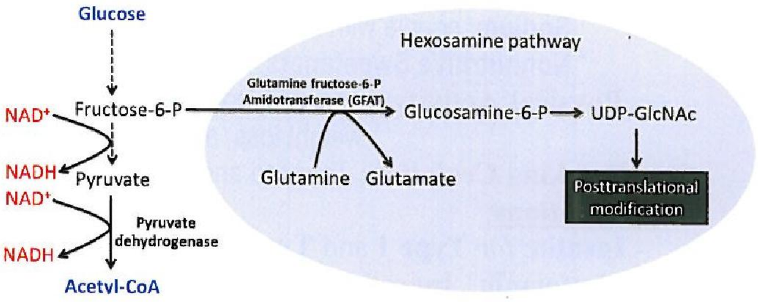
B) *Accumulation* of AGEs;

- **Advanced Glycation End Products (AGEs)** are ***proteins*** or ***lipids*** that *become* ***non-enzymatically* glycated** and **oxidized** after ***exposure*** to **aldose sugars (Glucose)**.
- ***Chronic* hyperglycemia** → ***accumulation*** of **AGEs** → ***contribute*** to a *variety* of **microvascular** and **macrovascular *complications***.


Glucose
Body and cell proteins
Schiff's base
Amadori products
AGE
Toxic
Hours
Days
Weeks and months

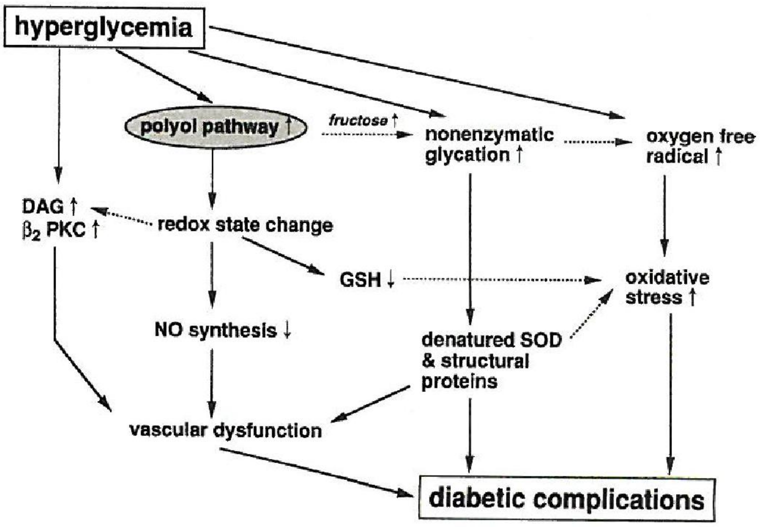
C) Hexosamine Pathway;

- This **pathway** *involves* ***formation*** of **Uridine Diphosphate N-acetylglucosamine (UDP-GlcNAc)** that is the ***substrate*** for **protein translational modifications** (*many changes* in ***both*** **gene** and **protein *levels***, which **together** *contribute to* the **pathogenesis** of **diabetic complications**).


Glucose
Hexosamine pathway
Glutamine fructose-6-P Amidotransferase (GFAT)
NAD⁺
Fructose-6-P
Glucosamine-6-P
UDP-GlcNAc
NADH
Pyruvate
Glutamine
Glutamate
Posttranslational modification
NAD⁺
Pyruvate dehydrogenase
NADH
Acetyl-CoA

D) Protein Kinase C (PKC) Pathway;

- **PKC *consists*** of a **family** of ***multifunctional*** **serine/threonine kinases**, which are ***involved*** in the ***control*** of other **proteins**.
- *At least* **12 PKC *isoforms***.
- The ***activities*** of the **classical isoforms** (PKC-α, -β1/2, and PKC-δ) are ***greatly*** **enhanced by Diacylglycerol (DAG)**, and have been *linked to* **vascular dysfunctions** and ***pathogenesis*** of **diabetic complications**.


hyperglycemia
polyol pathway ↑
fructose ↑
nonenzymatic glycation ↑
oxygen free radical ↑
DAG ↑
β₂ PKC ↑
redox state change
GSH ↓
oxidative stress ↑
NO synthesis ↓
denatured SOD & structural proteins
vascular dysfunction
diabetic complications

- **All these *mechanisms*** and **events** act in ***conjunction*** in **several ways**…….

- ***Treatments***;

A) **Treatment Goals**;

- Maintain daily ranges of blood glucose concentrations so that activities of daily living are not inhibited.
- Prevent the occurrence and/or progression of long-term macrovascular and microvascular complications.
- Ideally, meet A1C goals; Less than 7.5%.
- Prevent acute complications.
    - Monitor for hyperglycemia and hypoglycemia.
    - Minimize the adverse drug reactions of medications.
- Screen for and control other comorbidities: Hyperlipidemia, hypertension, nephropathy, retinopathy, hypothyroidism, celiac disease.
- Incorporate and foster self-management.
    - Age- and ability-appropriate self-management goals.
    - Meet patient's expectations.

B) **Life-Style Modifications**; All people with diabetes should participate in diabetes self-management education (DSME) and diabetes self-management support (DSMS) programs to facilitate the knowledge, skills, and abilities necessary for optimal diabetes self-care and incorporate the needs, goals, and life experiences of the person with diabetes.

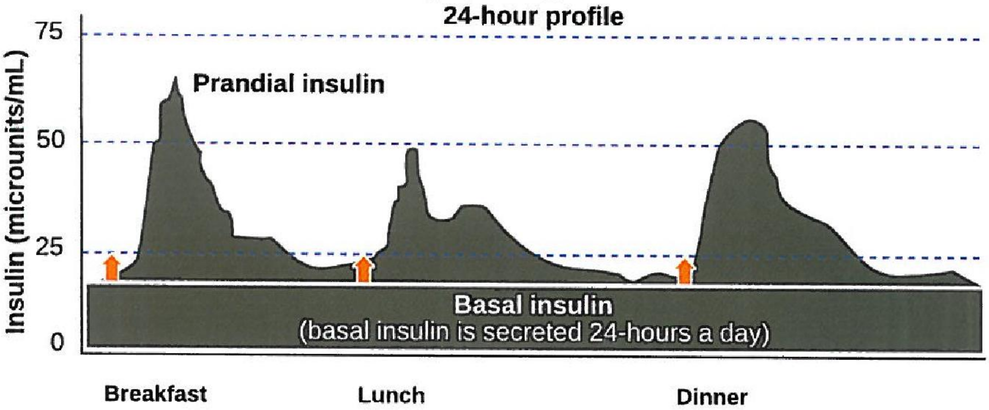
- **Weight Management**; can delay the progression from prediabetes to type 2 diabetes.
- **Alcohol Consumption**; risk of hypoglycemia weight gain and hyperglycemia.
- **Nutrition Therapy**;
    - * **Carbohydrate**; Education on how to use **Carbohydrate Counting**;
        - Help patients with diabetes plan meals.
        - Patients need to be aware of the amount of carbohydrates they eat.
        - Patients count all the carbohydrates in each meal and snack they eat.
        - Able to adjust their insulin dose according to the amount of carbohydrates eaten.
        - Allows for better blood glucose control.
    - * **Protein**; Ingested protein appears to increase insulin response without increasing plasma glucose concentrations; should not be used to treat or prevent hypoglycemia.
    - * **Dietary fat**; foods rich in long-chain omega-3 fatty acids is recommended to prevent or treat CVD.
    - * **Sodium**; people with diabetes should limit sodium consumption to 2,300 mg/day.
    - * **Nonnutritive Sweeteners**; reduce overall calorie and carbohydrate intake.
- **Physical Activity**; improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being.
- **Smoking Cessation**; Tobacco and e-cigarettes; heightened risk of diabetic complications.

C) **Medications**;

- **Insulin**: *for* **Type 1** and **Type 2 DM**.
- **Metformin** , **Incretin Mimetics** and **Oral Antidiabetic Drugs**; *for* **Type 2 DM**.

I) Insulin Preparations

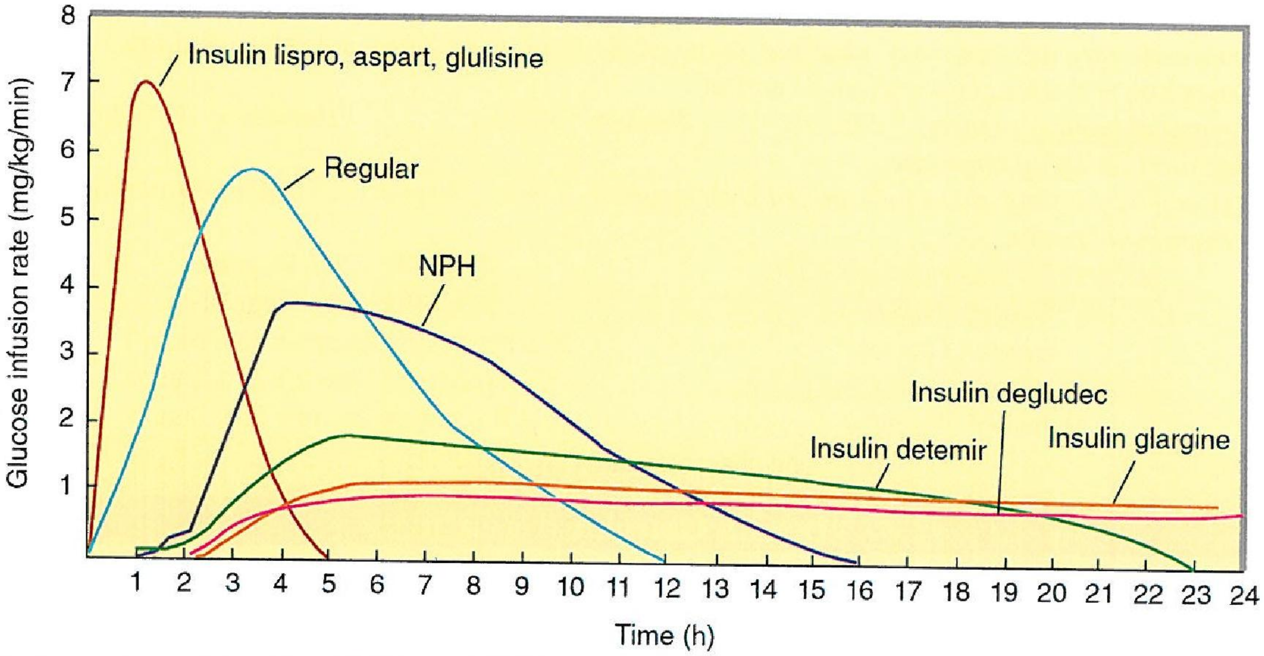
- **Insulin preparations** can ***mimic*** the ***normal*** **physiologic release** of **insulin**.



endogenous insulin secretion

- **Insulin preparations**;

Preparation		Species Source	Pattern
Short-acting Insulin	Regular Human Insulin	Human	Bolus
Rapid-acting Insulin	Insulin Aspart Insulin Lispro Insulin Glulisine	Human Analogue	Bolus
Intermediate-acting Insulin	Neutral Protamine Hagedorn (NPH)	Human	Bolus/Basal
Premixed Insulin	NPH/Regular Protamine/Rapid-acting	Human Human Analogue	Bolus/Basal
Long-acting Insulin	Insulin Glargine Insulin Detemir Insulin Degludec (ultra-long)	Human Analogue	Basal



A) Short-acting Insulin (Natural Insulin)

Soluble Insulin or Regular Insulin (Humulin® R) (Novolin® R) (Actrapid®)

- **Soluble Insulin** or **Regular Insulin** is a ***soluble*** **crystalline Zinc Insulin** that is *made by* **rDNA techniques**.
- ***Pharmacokinetics***; - ***Onset***; 30-60 minutes. - ***Peak***; 2-4 hours. - ***Duration***; 4-8 hours.
- ***Uses***; - **Used** to ***control*** the **Postprandial Hyperglycemia** (**Bolus ONLY**).
  - **Regular Insulin** can be used as **IV** in **emergency**.
- ***Time of Administration***; - **30-60 minutes *before* meal.**
  - ☝ **Patient *must* eat** (to ***avoid*** **hypoglycemia**).

B) Rapid-acting Insulin (Human Analogue)

Insulin Aspart (NovoRapid®) | Insulin Lispro (Humalog®) | Insulin Glulisine (Apidra®)

- **Insulin Aspart** [AS-part] is an **Insulin *analogue*** in *which* a ***single*** **substitution** of **Proline** by **Aspartic acid** at ***position*** **B28**.
- **Insulin Lispro** [LIS-proe] the **Proline** at ***position*** **B28** is ***reversed*** *with* the **Lysine** at **B29**.
- **Insulin Glulisine** [gloo-LYSE-een] **differs *from human*** **Insulin** in that the **amino acid Asparagine** at ***position*** **B3** is ***replaced by*** **Lysine** and the **Lysine** in ***position*** **B29** by **Glutamic Acid**.

- They are ***preferred*** to **Regular Insulin** *because* of ***faster*** **onset** and ***shorter*** **duration**, ***better*** **mimicking physiological need *during* postprandial period**.
- ***Pharmacokinetics***;
  - **Insulin Aspart**; - ***Onset***; 5-15 minutes. - ***Peak***; 1-2 hours. - ***Duration***; 3-5 hours.
  - **Insulin Lispro**; - ***Onset***; 5-15 minutes - ***Peak***; 0.5-2 hours. - ***Duration***; 3-5 hours.
  - **Insulin Glulisine**; - ***Onset***; 15-20 minutes. - ***Peak***; 0.75-1 hours. - ***Duration***; 4-5 hours.
- ***Uses***; - **Used** to ***control*** the **Postprandial Hyperglycemia** (**Bolus ONLY**).
  - **Insulin Aspart** can be used as **IV** in **emergency**.
- ***Time of Administration***; - **5-15 minutes *before* meal**; **just before** or **with** a **meal**.
  - ☝ **Patient *must* eat** (**Act *very quickly* hypoglycemia *occur* if *not* eat**).

C) Intermediate-acting Insulin (Neutral Protamine Hagedorn; NPH) (Isophane)

Insulin NPH (Insulatard®) (Humulin® N)

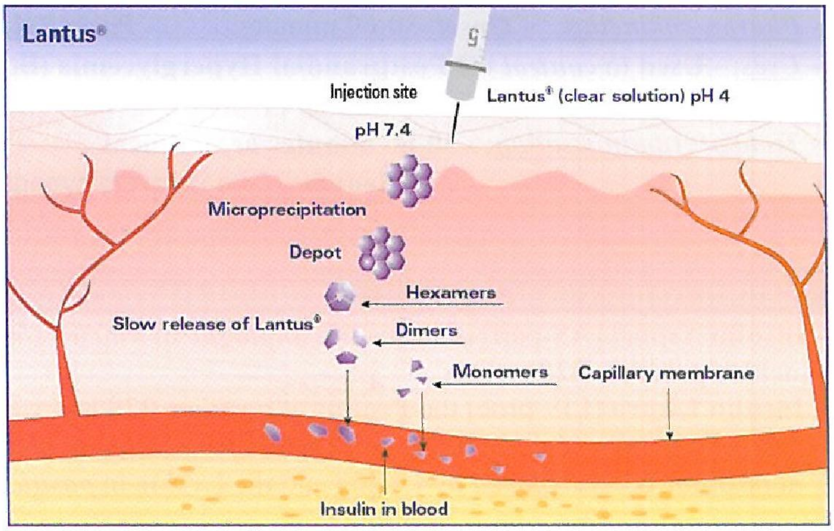
- In 1936, Hagedorn and B. Norman Jensen discovered that the effects of injected insulin could be prolonged by the addition of protamine, so that neither is present in an uncomplexed form (Isophane). After subcutaneous injection proteolytic tissue enzymes degrade the protamine to permit absorption of insulin.
- **Neutral Protamine Hagedorn (NPH)** is a ***suspension*** **(Cloudy/milky)** of ***crystalline*** **Zinc Insulin** ***combined with*** the *positively* ***charged*** *polypeptide* **Protamine**; ***less*** **soluble**, resulting in ***delayed*** **absorption** and a ***longer*** **duration** of **action**.
- ***Pharmacokinetics***; - ***Onset***; 1-2 hours. - ***Peak***; 5-10 hours. - ***Duration***; 10-16 hours.
- ***Uses***; used for **basal** ***coverage***.
- **NPH** and **Protamine** are *usually* ***mixed*** with **Regular**, **Lispro**, **Aspart**, or **Glulisine Insulin**;
  - ***Premixed*** **Insulin**;

Mixtard® 70/30 or Humulin® 70/30	70% **NPH** + 30% **Regular**
Mixtard® 50/50	50% **NPH** + 50% **Regular**
NovoMix® Flexpen	70% **Protamine Aspart** + 30% **Aspart**
Humalog® Mix 75/25	75% **Protamine Lispro** + 25% **Lispro**
Humalog® Mix 50/50	50% **Protamine Lispro** + 50% **Lispro**

D) Long-acting Insulin

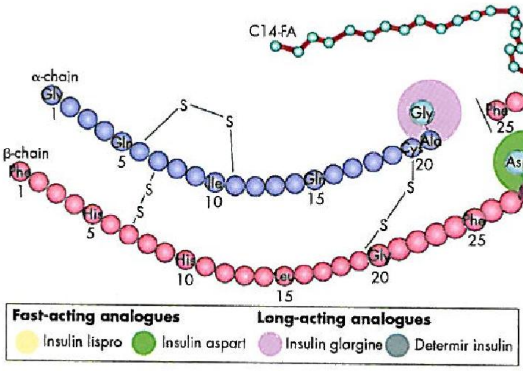
Insulin Glargine (Lantus®)

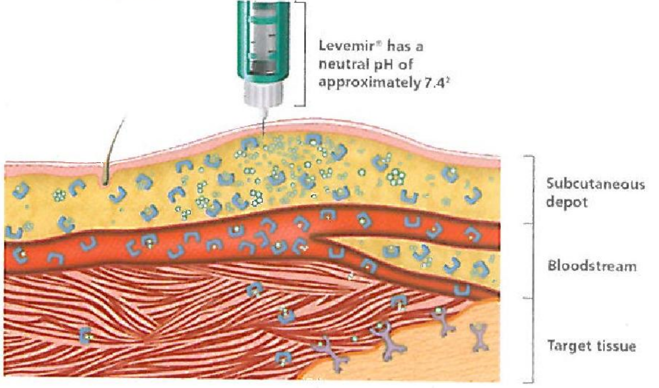
- **Insulin Glargine** [GLAR-geen] is a ***peakless*** (plasma concentration is plateau = **Basal**), ***long-acting*** **Insulin *analogue***.
- ***Pharmacokinetics***;
  - ***Onset***; 2 hours. - ***Peak***; **Peakless** (max. effect after 2–4 hours) - ***Duration***; $20\text{-}24^{+}$ hours.
  - To ***maintain*** **solubility**, the ***formulation*** is **acidic** (pH 4.0), and **Insulin Glargine *should not*** be **diluted** or **mixed** with ***other*** **Insulin** or ***solution*** in the ***same*** **syringe**.
  - **Glargine** is ***usually*** given **once daily** (Some patients on low doses require twice-daily dosing).
- **Injection-site reactions** (e.g., edema, itching, pain, stinging); because of acidic formulation.
- The amino acid asparagine at position A21 is replaced by glycine, and two arginines are added to the C-terminus of the B-chain. These changes shift the isoelectric point, producing a solution that is completely soluble at a pH of 4.
- When injected into the subcutaneous tissue, the acidic solution is neutralized (pH 7.4).
- This leads to the formation of microprecipitates, which small amounts of Lantus® are slowly released.
- The slow dissolution of free hexamers results in the lack of a peak and longer duration of action.



Insulin Detemir (Levemir®)

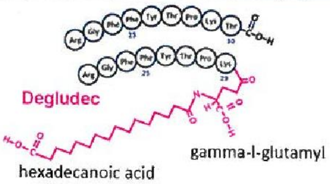
- **Insulin Detemir** [deh-TEE-meer] is a ***long-acting* Insulin *analogue*** in which a **fatty acid (Myristic acid)** is *bound to* the **Lysine amino acid** at ***position* B29**. The **fatty acid *side chain*** that ***enhances* association** to **albumin**. ***Slow* dissociation** *from* **albumin** *results in* ***long-acting* properties**.
- ***Pharmacokinetics***;
  - ***Onset***; 1-2 hours. - ***Peak***; **Peakless** (max. effect after 4–8 hours) - ***Duration***; 10-24 hours.
  - **Detemir *should not*** be **diluted** or **mixed** with ***other* Insulin** or ***solution*** in the ***same* syringe**.
  - ***Smoother* activity profile** and ***less* weight gain** *compared with* **NPH** and **Glargine**.
  - It is ***used* once** or **twice** a day to *achieve* a ***stable* basal coverage**.


C14-FA
α-chain
β-chain
Gly
Phe
Gln
Ile
Glu
Gly
Cys
Asn
His
Leu
Lys
Thr
Pro
Asp
Arg
Gly
Phe
1
5
10
15
20
25
29
30
Fast-acting analogues
Insulin lispro
Insulin aspart
Long-acting analogues
Insulin glargine
Determir insulin


Levemir® has a neutral pH of approximately 7.4²
Subcutaneous depot
Bloodstream
Target tissue

Insulin Degludec (Tresiba®)

- **Insulin Degludec** [de-GLOO-dek] is an ***ultra-long-acting* Insulin *analogue*** in which a **Threonine** at ***position* B30** has been ***removed*** and the **Lysine** at ***position* B29** is ***conjugated to* hexadecanoic acid** via a **gamma-l-glutamyl** *spacer*.
- **Insulin Degludec** was **FDA approved** in 25 September **2015**.
- ***Duration* of *action*** is ***more than* 42 hours** (***ultra-long-acting***).
- In the **vial**, in the presence of **Phenol** and **Zinc**, the **Insulin** is in the form of **dihexamers *but***, when ***injected* SC**, it *self-associates* into ***large* multihexameric** *chains consisting of* **thousands** of **dihexamers**.


Degludec
hexadecanoic acid
gamma-l-glutamyl

E) Inhaled Insulin

Inhalable Insulin (Afrezza®)

- A ***dry* powder** *formulation* of ***recombinant* Regular Insulin** is *now* ***approved*** for use in **adults** with **diabetes**.
- ***After* inhalation**; ***peak* levels** are *reached* in **12–15 minutes** and ***decline*** to **baseline** in **3 hours**; ***faster*** in **onset** and ***shorter*** in **duration** than **SC Insulin**.
- It is ***formulated*** as a ***single-use* color *coded* cartridge** *delivering* **4**, **8** or **12 units *immediately*** *before* the **meal**.
  - 4-unit cartridge = 4 units of rapid-acting insulin.
  - 8-unit cartridge = 5–8 units of rapid-acting insulin.
  - 12-unit cartridge = 9–12 units of rapid-acting insulin.

4-units
8-units
12-units

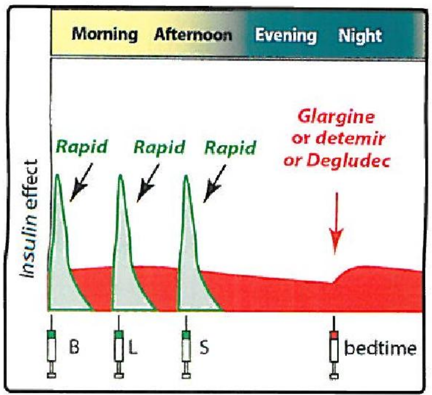
- ***Insulin Action***;

Insulin	Onset	Peak	Duration
Regular	30–60 min	2–4 hr	4–8 hr
Aspart	5-15 min	1–2 hr	3–5 hr
Lispro	5–15 min	0.5–2 hr	3–5 hr
Glulisine	15–20 min	0.75–1 hr	4–5 hr
NPH	1–2 hr	5–10 hr	10–16 hr
Glargine	2 hr	Flat	20–24⁺ hr
Detemir	1–2 hr	Flat	10–24 hr
Degludec	1–2 hr	Flat	>42 h

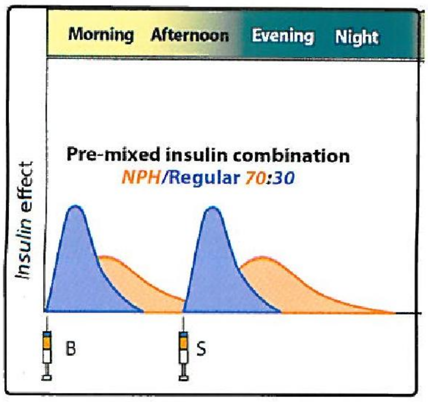
Principles of Insulin Therapy

[**Basal/Bolus Insulin regimen** is ***recommended***]

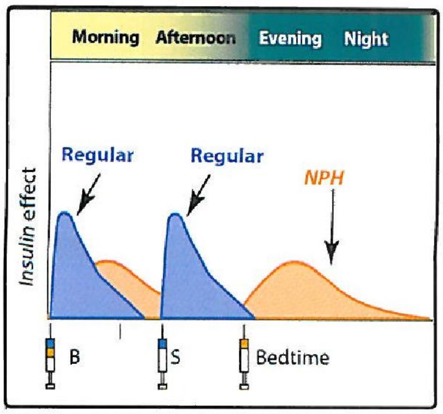
- **Multiple Daily Injection** (**MDI**) ***Regimen***;



≥ 4 injections per day



2 injections per day



3 injections per day

MDI Regimen	Advantages	Disadvantages
≥ 4 injections per day [long-acting for basal coverage] + [rapid-acting for bolus coverage]	- Meal times can vary. - Carbohydrate intake can vary. - Less insulin overlap. - Usually best injectable option for blood glucose control because it closely mimics physiologic insulin release. - Less blood glucose variability.	- Several injections each day. - May be difficult for some patients because of the math and problem solving required for flexible dosing. - More costly than an NPH regimen.
2 injections per day [short-acting for bolus] + [NPH for basal & bolus] (Mixing 2 insulins together in a syringe results in single injections at breakfast and dinner)	- Only 2 injections each day. - No injections at school for lunch. - Less chance of forgetting. - Easier to learn fixed dosing than MDI flexible dosing. - Cheaper.	- Does not mimic physiologic release of insulin very well. - Requires meals to be at certain times. - Requires constant/consistent carbohydrate intake. - Snacks needed. - Greater risk of hypoglycemia, especially overnight. - Difficult to achieve treatment goals.
3 injections per day [short-acting + NPH for breakfast; single injection] + [short-acting for dinner] + [NPH for bedtime]	- Decreases the risk of overnight hypoglycemia compared with the 2-injection NPH regimen. - Less than 4 injections a day. - Better control of dawn phenomenon than the 2-injection NPH regimen. - No midday injection for food; however, a correctional dose may be needed at times.	- Requires meals to be at certain times. - Requires constant/consistent carbohydrate intake. - Snacks needed. - More than 2 injections daily. - Difficult to achieve treatment goals.

- *Initiating* **Insulin Therapy**;
  - **Total Daily Dose (TDD) Insulin *requirement*; *Initially*; 0.3–0.5 unit/kg/day.**
    - A) **NPH** 2- or 3-**injection regimen**; For example; TDD = 15 IU

2/3 of TDD in the morning (10 Units)		1/3 of TDD in the evening (5 U)	
2/3 NPH (7 Units)	1/3 rapid (3 Units)	2/3 NPH (3 Units)	1/3 rapid (2 Units)
		OR	
		1/2 NPH (2.5 Units)	1/2 rapid (2.5 Units)

B) ***Long-acting* Insulin** in a **basal/bolus regimen** in **≥ 4-injection regimen**; About 50% of TDD.
  - New onsets and small children may require only 30% basal coverage.
  - Example of glargine dose for TDD of 15 units: 50% of 15 units/day = 7.5 units.

1/2 of TDD	1/2 of TDD
1/2 of TDD is bolus Insulin	1/2 of TDD is Long-acting Insulin

C) ***Short-acting* Insulin** in a **basal/bolus regimen** in **≥ 4-injection regimen**;
  1) **Fixed dosing**; dividing the remaining % of TDD (about 1/2 of TDD) between meals equally.
  2) **Flexible dosing**; adjust dose according to predicted needs;
    - **I:CHO**; the amount of carbohydrates (grams), covered by 1 unit of insulin.
      - Carbohydrate ratio 1:15 = 1 unit of insulin will displace 15 g of carbohydrates.
    - **Insulin Sensitivity Factor (ISF)** or **Correction Factor**; is the amount of reduction in blood glucose per 1 unit of insulin; lower blood glucose to a specified target amount.
      - Example; ISF of 50 (1:50) means 1 unit of insulin will reduce blood glucose by 50 mg.

Initiating an I:CHO

[The 500 Rule]

- 500/TDD = grams covered by 1 unit of short-acting insulin
- Example; A patient requires 65 units of insulin a day:
  - 500/65 = 7.69 equals about 7.5, so 1:7.5 I:CHO

Initiating an ISF

[The 1800 Rule; for rapid insulin]

- 1800/TDD = mg/dL reduced by 1 unit of rapid-acting insulin.
- Example; A patient requires 65 units of insulin a day:
  - 1800/65 = 27.69 equals about 30, so 30 ISF (1:30 correction factor)

[The 1500 Rule; for regular insulin]

- 1500/TDD = mg/dL reduced by 1 unit of rapid-acting insulin.
- Example; A patient requires 65 units of insulin a day:
  - 1500/65 = 23, so 23 ISF (1:23 correction factor)

- **Example case**;
  - A patient is about to eat his lunch, which has 89 g of carbohydrates, and his blood glucose is 210 mg/dL;
    - He uses the following: - I:CHO of 1:7.5 - ISF of 30; target of 120.
      - * Food: 89 (g of carbohydrates)/7.5 (I:CHO) = 11.86 equals about 12 units for carbohydrates
      - * Correction: 210 − 120 (target) = 90 mg/dL too high; 90/30 (ISF) = 3 units correction
      - * Bolus dose: 12 (for food) + 3 (for correction) = 15 units required.

Medications for Type 2 Diabetes

- **Medications for Treatment of Type 2 Diabetes**;
  - **A) Metformin**; *for **all*** **patients.**
  - **B) *Oral* Antidiabetic Drugs**; *such as* **Sulfonylureas.**
  - **C) Glucagon-like peptide-1 (GLP-1) Agonists**; are injectable agents.
  - **D) Pramlintide** (Symlin®); is an injectable **Amylin *analogue***.
  - **E) Insulin**; ***Add* Insulin** if; **A1C** is **> 9%** or **blood glucose levels** are **> 250 mg/dL**.
    - *May be* **basal *alone*** or **basal/bolus regimen.**
    - **Basal/bolus regimen** may be ***considered*** *if*; **A1C > 10%**, **blood glucose > 350 mg/dL** or **patient** has **DKA.**
    - ***Initiate*** **basal-*alone* regimen** at **0.25 unit/kg.**
    - ***Intensify*** **treatment** if **blood glucose** and **A1C goals** are ***not*** **met.**
    - **Insulin** *may be* ***tapered*** **over time** as ***control*** **improves** and ***possibly*** **discontinued.**

Antidiabetic Drugs

I) Insulin

Regular Insulin (Humulin® R)
Insulin Aspart (NovoRapid®)
Insulin Lispro (Humalog®)
Insulin Glulisine (Apidra®)
Insulin NPH (Insulatard®)
Insulin Glargine (Lantus®)
Insulin Detemir (Levemir®)
Insulin Degludec (Tresiba®)
Inhalable Insulin (Afrezza®)

II) Insulin Secretagogues

Sulfonylureas

First Generation

Tolbutamide (Orinase®)
Tolazamide (Tolinase®)
Acetohexamide (Dymelor®)
Chlorpropamide (Diabinese®)
Carbutamide (Glucidoral®)

Second Generation

***Glibenclamide** or **Glyburide** (Daonil®)
***Glimepiride** (Amaryl®)
***Glipizide** (Minidiab®)
***Gliclazide** (Diamicron®)
Gliquidone (Glurenorm®)
Glibornuride (Glutril®)
Glyclopyramide (Deamelin-S®)

Meglitinides

***Repaglinide** (NovoNorm®)
***Nateglinide** (Starlix®)
Mitiglinide (Glufast®)

III) Insulin-Sensitizers

Biguanides

Metformin (Glucophage®)

Thiazolidinediones

Pioglitazone (Actos®)

Rosiglitazone (Avandia®)

Glitazars

Saroglitazar (Lipaglyn®)

IV) Peptide Analogues

Injectable Incretin Mimetics [Glucagon-like peptide-1 Agonists]

Exenatide (Byetta®)
Liraglutide (Victoza®)
Lixisenatide (Lyxumia®)
Albiglutide (Tanzeum®)
Dulaglutide (Trulicity®)
Semaglutide (Ozempic®)

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin (Januvia®)
Vildagliptin (Galvus®)
Saxagliptin (Onglyza®)
Linagliptin (Tradjenta®)
Alogliptin (Nesina®)

Injectable Amylin Analogues

Pramlintide (Symlin®)

V) Glycosurics

Sodium/Glucose Co-transporter-2 (SGLT2) Inhibitors

Dapagliflozin (Farxiga®) (Forxiga®)
Canagliflozin (Invokana®)
Empagliflozin (Jardiance®)
Ertugliflozin (Steglatro®)

VI) Alpha-glucosidase Inhibitors

Acarbose (Glucobay®)
Miglitol (Glyset®)
Voglibose (Voglib®)

VII) Others

Bile Acid Sequestrants

Colesevelam (Welchol®)

Dopamine Agonists

Bromocriptine (Cycloset®)

II) Insulin Secretagogues

1) Sulfonylureas

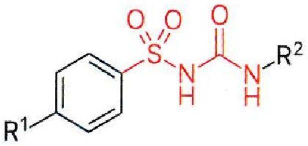
First Generation

- **Tolbutamide** (Orinase®)
- **Tolazamide** (Tolinase®)
- **Acetohexamide** (Dymelor®)
- **Chlorpropamide** (Diabinese®)
- **Carbutamide** (Glucidoral®)

Second Generation

- **Glyburide** or **Glibenclamide** (Daonil®)
- **Glipizide** (Minidiab®)
- **Gliquidone** (Glurenorm®)
- **Glyclopyramide** (Deamelin-S®)
- **Glimepiride** (Amaryl®)
- **Gliclazide** (Diamicron®)
- **Glibornuride** (Glutril®)
- **Glisoxepide**

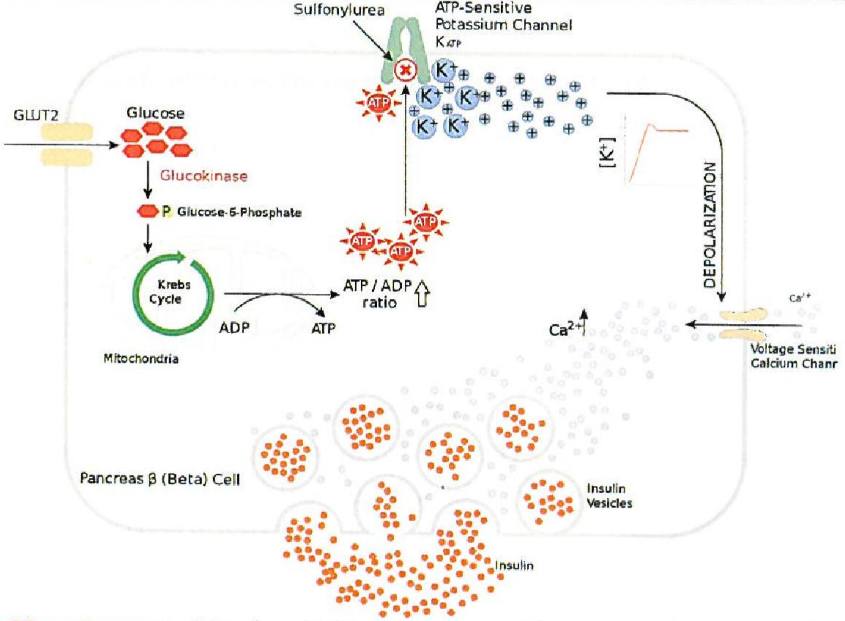
- These agents are classified as **insulin secretagogues**, *because* they ***promote*** **Insulin *release*** from the **β cells** of the **pancreas**.
- The **sulfonylureas** in ***current*** **use** are the **second-generation *drugs*** (***good*** **pharmacokinetic profile**, ***more*** **potent** and ***less*** **side effects**).
- **Glyburide** [GLYE-byoor-ide], **Glipizide** [GLIP-ih-zide] and **Glimepiride** [GLYE-me-pih-ride] are the ***only*** **sulfonylureas** ***currently*** *available* in **United States**.


O
O
O
S
N
H
N
H
R2
R1

Sulfonylurea group (red)

- ***Dose*** (**Second-generation**); *usually* **once daily** *with* **breakfast** or ***first main*** **meal** of the day.
- **Glimepiride** is ***approved*** for **once-daily use** as ***monotherapy*** or in ***combination*** with **Insulin**.

Mechanism OF Action


Sulfonylurea
ATP-Sensitive Potassium Channel K ATP
K+
ATP
GLUT2
Glucose
Glucokinase
P Glucose-6-Phosphate
Krebs Cycle
Mitochondria
ADP
ATP
ATP / ADP ratio
[K+]
DEPOLARIZATION
Ca2+
Voltage Sensiti Calcium Chanr
Pancreas β (Beta) Cell
Insulin Vesicles
Insulin

- **Sulfonylureas** ***block*** **ATP-sensitive K^+ channels**, ***resulting*** in **depolarization**;
  - **Depolarization** ***opens*** a **voltage-gated calcium channel** and ***results*** in **Ca^{2+} *influx*** and the ***release*** of *preformed* **Insulin** by ***exocytosis***.
- *In addition*, **Sulfonylureas** may ***reduce*** **hepatic Glucose *production*** and ***increase*** *peripheral* **Insulin *sensitivity***.

Pharmaco Kinetics

- **Sulfonylureas** are ***given*** **orally**, these drugs ***bind*** to **serum proteins**, are ***metabolized*** by the **liver**, and are ***excreted*** in the **urine** and **feces**.
- ***Duration*** of ***action*** of **second-generations** are **ranges** *from* **12** to **24 hours**.
- ***Micronized*** **Glyburide** (Glynase® PresTab®) is ***available*** (faster in onset).
- **Glipizide *extended-release*** **formulation** (Glucotrol XL®) is ***available*** (provides 24-hour action after a once-daily morning dose).
- **Second-generations** are *usually* ***combined*** with **Metformin**.

Side Effects

- *Major* **side effects**; **Weight gain**, **hyperinsulinemia** and **hypoglycemia**.
- **Used** with ***caution*** in **hepatic** or **renal insufficiency** (accumulation of sulfonylureas may cause hypoglycemia);
  - *Increase* the **risk** of **hypoglycemia** with **Glyburide** in **renal impairment**.
  - **Glipizide** or **Glimepiride** are safer in renal dysfunction and in elderly patients.
- **Glyburide** has ***minimal*** **transfer** *across* the **placenta** and *may be* **allowing** a **safe** ***new*** **treatment** for **Gestational Diabetes**.

Drug Interactions

↓ Sulfonylureas effects	↑ Sulfonylureas effects (hypoglycemia)
Atypical antipsychotics	**Azole antifungals** **β-blockers**
Corticosteroids	**Chloramphenicol**
Diuretics	**Clarithromycin** **Monoamine Oxidase Inhibitors**
Niacin	**Probenecid**
Phenothiazines	**Salicylates**
Sympathomimetics	**Sulfonamides** **Warfarin**

2) Meglitinides "Glinides"

Repaglinide (NovoNorm®)	**Nateglinide** (Starlix®)	**Mitiglinide** (Glufast®)

- *This* **class** of **drugs**, also *known as* the ***Non*-sulfonylurea Secretagogues**.
- **Meglitinides** act on the ***same*** **β-cell receptor** as **Sulfonylureas** (same mechanism) *but* have a ***different*** **chemical structure** with ***rapid*** **onset** and a ***short*** **duration** of **action**;
  - There is ***no*** **sulfur** in its **structure**, so they may use in **type 2 diabetics** with **sulfur** or **sulfonylurea** ***allergy***.
- **Repaglinide** [re-PAG-lin-ide] is the ***first*** **member** of the **Meglitinides**.
- **Nateglinide** [nuh-TAY-gli-nide] is a **D-phenylalanine derivative**.
- **Mitiglinide** [mee-TE-gli-nide] is a **benzyl-succinic acid derivative**; like **Repaglinide** & **Nateglinide**, it is ***bind*** to the **sulfonylurea receptor**, but it has been ***approved*** for use in **Japan**.

Pharmaco Kinetics

- ***Rapid* onset** and ***short* duration** of **action**;
  - NovoNorm® available as tablets (white: 0.5 mg; yellow: 1 mg; peach: 2 mg), dose; **15 minutes** ***before*** each main meal; max. daily dose: 16 mg per day.
  - ***Risk*** of **hypoglycemia** if **meal** is ***delayed*** or ***skipped*** or ***inadequate*** **carbohydrate**.
- They are **metabolized** to **inactive** ***products*** by **CYP450**;
  - **Repaglinide** → CYP3A4.
  - **Nateglinide** → CYP2C9 and CYP3A4.
- **Excretion** ***mainly*** in **feces** *via* **bile**;
  - It ***can*** be **used** in **patients** with **renal impairment** and in the **elderly**.
  - ***Should*** be **used** with ***caution*** in **patients** with **hepatic impairment**.

Side Effects

- *Major* **side effects**; **Weight gain** & **hypoglycemia** (less than sulfonylureas).
- **Meglitinides** ***should not*** be **combined** *with* **Sulfonylureas**, *because* they have the ***same*** **mechanism** *of* **action**; ***risk*** of **hypoglycemia**.

Drug Interactions

- **Drugs** that ***inhibit*** **CYP3A4**; such as **Itraconazole**, **Fluconazole**, **Erythromycin** and **Clarithromycin** → may ***enhance*** the **glucose** ***lowering*** **effect** of **Repaglinide** (hypoglycemia).
- **Drugs** that ***induce*** **CYP3A4**, such as **Barbiturates**, **Carbamazepine** and **Rifampin** → may ***decrease*** **effect** of **Repaglinide**.
- **Gemfibrozil** ***increase*** the **effects** of **Repaglinide**.

III) Insulin-Sensitizers

1) Biguanides

Metformin (Glucophage®)

- The **Insulin-Sensitizers** are *class* of **drugs** that *enhance* the **Insulin** *sensitivity* in **peripheral tissues** (**muscle**, **fat** and **liver**); *decrease* **insulin resistance** and *increases* **glucose uptake**.
- *Unlike* **Sulfonylureas**, **Insulin-Sensitizers** *does not promote* **Insulin secretion**;
  - Therefore, hyperinsulinemia is not a problem, and less risk of hypoglycemia.
- **Metformin** [met-FOR-min] is the *only* **biguanide** *currently* **available** (**Phenformin** and **Buformin** are ***withdrawn*** from the **market** *due to* **toxic effects**).

Pharmaco Kinetics

- ***Absorption***;
  - **Bioavailability; 50-60%**
  - ***Peak* plasma time**; - ***Regular-release***: 2-3 hours.
    - ***Extended-release***: 4-8 hours.
- ***Distribution***; - **Protein bound**: *Minimal* - **Half-Life**: 4-9 hours.
- ***Metabolism***; ***not* metabolized**.
- ***Excretion***; **Urine** (90 % by tubular secretion).

Mechanism OF Action

- A **full explanation** of the **mechanism** of **action** of the **Metformin** ***remains elusive***, but their ***primary* effect** is *mediated by* **activation** of **AMP-activated protein kinase** (**AMPK**); a liver enzyme that plays an important role in insulin signaling, whole body energy balance, and the metabolism of glucose and fats.
- ***Main Mechanisms* of *Action***;
  - * ***Suppressing* liver Glucose *production*** (↓ **hepatic gluconeogenesis**).
  - * ***Decreasing* intestinal absorption** of **Glucose**.
  - * ***Improving* Insulin sensitivity** by ***increasing* peripheral Glucose *uptake*** and ***utilization***.
- The ***rare*** **side effect lactic acidosis**, is thought to be *caused by* ***decreased* liver uptake** of ***serum* lactate**, one of the *substrates* of **gluconeogenesis**.

Therapeutic Uses

- **Type 2 Diabetes** (**first line therapy**; all patients).
- ***Off-Label Uses*** [**Decrease Insulin *Resistance***];
  - **Prediabetes**; decrease their chances of diabetes.
  - **Gestational Diabetes** (*safe as* **Insulin**); **US FDA Category B**.
  - **Polycystic Ovary Syndrome** (**PCOS**) and **Female Infertility**.
  - ***Prevention* of weight gain** *caused by* **antipsychotic medications**.
  - ***Not* yet *recommended for* weight loss**.
  - ***Reduce* risk** of **pancreatic cancer**.
  - ***Helps*** to ***reduce* LDL cholesterol** and **triglyceride levels**.

Dose

- ***Formulations***;
  - **Metformin IR** (**immediate release**); 500, 850 and 1000-mg tablets.
  - **Metformin SR** (**slow release**) or **XR** (**extended release**); 500, 750, and 1000-mg tablets; mainly to ***counteract*** *common* **GI side effects**.
  - **Metformin** is available as **fixed-dose combinations** with ***other*** **oral antidiabetic drugs**.
- ***Dose*** in **Type 2 Diabetes**;
  - ***Prescribed*** as **maximum tolerated dose** (until GI side effects occur but not more than 2500 mg/day), ***start* gradually**, **SR** or **XR** ***formulations*** has ***low* risk** for **GI side effects**.

Side Effects

- **Gastrointestinal Upset** (*including* **diarrhea, cramps, nausea, vomiting** and **flatulence**) occur in ***up to* 20%** of **patients**; **dose titration** ***recommended*** to **develop tolerance**.
- **Black Box Warning**; **Lactic Acidosis** (*rare, but potentially* **severe**) **risk** ***increases*** in **patients** with ***severe* renal impairment**.
- ***Long-term*** use may ***interfere*** with **Vitamin B12 *absorption***.

2) Thiazolidinediones (TZDs) "Glitazones"

Pioglitazone (Actos®) — Rosiglitazone (Avandia®)

- **Pioglitazone** [pye-oh-GLI-ta-zone] and **Rosiglitazone** [roe-si-GLIH-ta-zone] are the ***only*** **Glitazones** ***still*** *available* in ***some*** **countries.**
- **Troglitazone** (Rezulin®) is the ***first*** **TZDs**, it was ***withdrawn*** from the **market** *because* of **hepatic toxicity** thought to be *related to* its **side chain. Lobeglitazone** (Duvie®) *approved* for use in **Korea.**
- **Pioglitazone** (once daily) and **Rosiglitazone** (once daily OR 2 divided doses) are is *approved* as a ***monotherapy*** and in ***combination*** *with* **Metformin, Sulfonylureas** and **Insulin** for the ***treatment*** of **Type 2 Diabetes** (***not*** **first line; used in people who *can't* control their diabetes by *other* ways).**
- **TZDs** can **used** in ***combination*** *with* **Metformin** in **Polycystic Ovary Syndrome (PCOS).**

Pharmaco Kinetics

- ***Absorption***; ***Well*** **absorbed** *after* **oral administration.**
  - **Pioglitazone *absorbed within* 2 hours** (food may delay absorption).
  - **Rosiglitazone** is ***rapidly*** **absorbed.**
- ***Distribution***; **protein bound:** ***extensively*** **bound** to **albumin.**
- ***Metabolism***; **CYP450** (*primary* CYP2C8);
  - ***Should*** **be used with *caution* in patients with hepatic impairment.**
- ***Excretion***; - **Pioglitazone**; In the **feces** *via* **bile *excretion*.**
  - **Rosiglitazone**; *Primary* in the **urine.**

Mechanism OF Action

- **Thiazolidinediones** are ***ligand*** of **peroxisome proliferator-activated receptor-gamma (PPARγ)**, a ***group*** of **nuclear receptors** *found* in **muscles, adipose tissues** and **liver.**
- **PPARγ receptors *modulate*** the **expression genes** *involved in* **lipid** and **glucose *metabolism*, insulin signal *transduction*** and **adipocyte** and ***other*** **tissue differentiation.**
- ***Observed effects*** of the **Thiazolidinediones**;
  - ***Increased*** **glucose transporter *expression* (GLUT 1** and **GLUT 4).**
  - ***Decreased*** **free fatty acid** *levels.*
  - ***Decreased*** **hepatic glucose *output*.**
  - ***Increased*** **adiponectin** and ***decreased*** *release* of **resistin** from **adipocytes,** and ***Increased*** *differentiation* of **preadipocytes** *to* **adipocytes.**
- ***Effects*** of **Thiazolidinediones** on **plasma lipids.**
  - **Rosiglitazone** and **Pioglitazone** → ↑ **HDL cholesterol.**
  - **Rosiglitazone** → ↑ **LDL cholesterol,** *while* **Pioglitazone** → ↓ **Triglycerides.**

Side Effects

- **Liver toxicity** has been ***reported***; **Liver function tests *should be* performed.**
- **Fluid retention** (*worsen* **heart failure)** and **weight gain.**
- **Black Box Warning**; ***Risk*** *of* **Congestive Heart Failure** in ***some*** **patients.**
- ***Meta-analysis*** **Studies**;
  - * **Rosiglitazone** may ***increase*** **risk** of **Coronary Heart Diseases (angina** or **myocardial infarction).**
  - * **Pioglitazone** may ***associated*** with a ***slightly*** **higher risk** of **Bladder Cancer.**
- ***Reduce*** of **bone mineral density** and ***increase*** the **risk** of **fractures** in **women,** due to ***decreased*** **osteoblast *formation*.**

3) Dual PPAR agonists "Glitazar"

Saroglitazar (Lipaglyn®)

- **Saroglitazar** is ***novel first*** in class **drug** which ***acts*** as a ***Dual*** **PPAR agonist** at the ***subtypes*** **α** and **γ** of the **peroxisome proliferator-activated receptor (PPAR).**
- **Saroglitazar** was ***approved*** in **2013** in **India** for the ***treatment*** of **Type 2 Diabetes** and **Dyslipidemia.**
- **Saroglitazar** → ↑ **HDL cholesterol,** ↓ **LDL cholesterol** and ↓ **Triglycerides.**
- ***Side Effects***; ***According*** to the **data** in the official website of the drug "lipaglyn.com", It has ***no*** or ***less*** **side effects** (weight gain and edema) ***than*** **TZDs.**

IV) Peptide Analogues

1) *Injectable* Incretin Mimetics [Glucagon-like Peptide-1 Agonists]

Exenatide (Byetta®) (Bydureon®)	**Liraglutide** (Victoza®) (Saxenda®)
Lixisenatide (Lyxumia®) (Adlyxin®)	**Albiglutide** (Tanzeum®)
Dulaglutide (Trulicity®)	**Semaglutide** (Ozempic®)

- *Oral* **Glucose** ***results*** in a ***higher*** **Insulin** ***secretion*** *than* occurs ***equal*** *amount* of **Glucose** is **IV**. This is *because* the *oral* **glucose** causes a ***release*** of **gut hormones** (**Incretins**).
- *Mechanism of Action*; **Incretins** are ***responsible for*** 60-70% of ***postprandial*** **Insulin** ***secretion***.
    - **Glucagon-like Peptide-1** (**GLP-1**) & **Gastric Inhibitory Peptide** [or Glucose-dependent Insulinotropic Peptide] (**GIP**) are **Incretins** and **released** ***after*** **eating** → ↑ **Insulin** & ↓ **Glucagon** ***secretion***, ***slow*** **gastric emptying** *time*, ***reduce*** **food intake** by ***enhancing*** **satiety** (a feeling of fullness) and ***promote*** **β-cell** ***proliferation***.
    - **Incretins** is ***rapidly*** **degraded** ***by*** **Dipeptidyl Peptidase 4** (**DPP-4**) **enzyme**.
- **Exenatide** [EX-e-nah-tide], **Liraglutide** [LIR-a-GLOO-tide], **Lixisenatide** [LIX-i-SEN-a-tide], **Albiglutide** [al-bi-GLOO-tide], **Dulaglutide** [DOO-la-GLOO-tide] and **Semaglutide** [SEM-a-GLOO-tide] are ***injectable*** **Incretin Mimetics** (or **Glucagon-like Peptide-1 Agonists**) used for the ***treatment*** of **Type 2 Diabetes**. **Liraglutide** (**Saxenda**®); *approved for* **Obesity**; **BMI** of **≥ 30** or **≥27**.

Dose

- **Exenatide** (**Byetta**®); **SC injectable solution**; 5 µg/dose & 10 µg/dose SC pen;
    - *Dose*; 5 µg *twice* a day for 30 days may *increase to* 10 µg *twice* a day; *within* 1 hour *before* morning and evening meal.
- **Exenatide** (**Bydureon**®); **SC injectable suspension**; 2mg/vial or 2mg/Pen;
    - *Dose*; 2 mg SC *once* weekly.
- **Liraglutide** (**Victoza**®); 18mg/3mL **SC injectable pen**; delivers doses of 0.6mg, 1.2mg, or 1.8 mg; approved *for* **Type 2 Diabetes**;
    - *Dose*; 0.6 mg once daily for one week (only to decrease GI side effects and does not provide glycemic control) then increase to 1.2 mg once daily (If glycemic control not achieved, can increase to 1.8 mg once daily).
- **Liraglutide** (**Saxenda**®);18mg/3mL **SC injectable pen**; delivers doses of 0.6mg, 1.2mg, 1.8mg, 2.4mg or 3 mg; approved *for* **Obesity**;
    - *Dose*; 0.6 mg once daily for one week; increase by 0.6 mg daily at weekly intervals to a target dose of 3 mg once daily.
- **Lixisenatide** (**Lyxumia**®; Europe) (**Adlyxin**®; US);
    - 50mcg/mL in 3mL **SC injectable pen** (green pen); initial dose pen.
    - 100mcg/mL in 3 mL **SC injectable pen** (burgundy pen); Maintenance.
    - *Dose*; 10 mcg SC once daily for 14 days, Increase dose to 20 mcg SC once daily starting on Day 15.
- **Albiglutide** (**Tanzeum**®); 30mg/pen or 50mg/pen (single-use injectable pen).
    - *Dose*; 30 mg SC once weekly; may increase to 50 mg once weekly if glycemic response is inadequate.
- **Dulaglutide** (**Trulicity**®); 0.75mg/0.5mL pen or 1.5mg/0.5mL (single-use).
    - *Dose*; 0.75 mg SC once weekly, may increase dose to 1.5 mg once weekly for additional glycemic control.
- **Semaglutide** (**Ozempic**®); 1.34mg/mL; delivers doses of 0.25mg, 0.5mg, or 1mg
    - *Dose*; 0.25 mg SC once weekly for 4 weeks initially; THEN increase the dosage to 0.5 mg once weekly, If glycemic control not achieved after at least 4 weeks on 0.5-mg dose, can increase to 1 mg once weekly.

- *Common Side Effects*; **Injection-site nodule** and **reactions, nausea, vomiting & diarrhea**.
- **Block Box Warning**; ***increased*** *incidence of* **Medullary Thyroid Carcinoma** (**MTC**) [**C-cell** or **Parafollicular** *tumors*] ***serum*** **Calcitonin** or **thyroid ultrasound** ***monitoring*** *are needed*.
- *Increased* **risk** of **pancreatitis** (***unexplained persistent severe*** **abdominal pain**); *due to* **proliferative effects** in the **pancreas**.

2) Dipeptidyl Peptidase-4 (DPP-4) inhibitors "Gliptins"

Sitagliptin (Januvia®)	**Vildagliptin** (Galvus®)	**Saxagliptin** (Onglyza®)
Linagliptin (Tradjenta®)	**Alogliptin** (Nesina®)	**Gemigliptin** (Zemiglo®)
Anagliptin (Suiny®)	**Teneligliptin** (Tenelia®)	**Trelagliptin** (Nesina®)
Omarigliptin (Marizev®)	**Evogliptin** (Suganon®)	**Gosogliptin** (SatRx®)

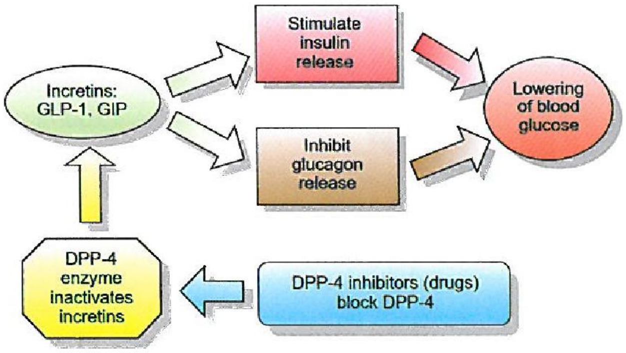
- **Sitagliptin** [si-ta-GLIP-tin], **Saxagliptin** [saxa-GLIP-tin], **Linagliptin** [lin-a-GLIP-tin], **Alogliptin** [al-oh-GLIP-tin] are the ***only*** **DPP-4 inhibitors** *approved by* **US FDA**.
- **Vildagliptin** [vil-da-GLIP-tin] is ***approved*** in **European Union (EU)**.
- **Gemigliptin** (approved in Korea), **Anagliptin** (approved in Japan), **Teneligliptin** (approved in Japan), **Trelagliptin** (approved in Japan), **Omarigliptin** (approved in Japan; once-weekly), **Evogliptin** (approved in South Korea) and **Gosogliptin** (approved for use in Russia).
- **DPP-4** ***inhibitors*** used in **Type 2 Diabetes** as ***monotherapy*** or in ***combination*** with **Metformin**, **Thiazolidinediones** or **Sulfonylureas**.
- ***Fixed dose combination*** *examples*;
  - **Sitagliptin** + **Metformin** (**Janumet®** 50/500, 50/850, 50/1000 mg); ***twice*** **daily** *with* **meals**.
  - **Sitagliptin** + **Metformin XR** (**Janumet® XR** 50/500, 50/1000, 100/1000 mg); ***once*** **daily** *with* **meals**.
  - **Vildagliptin** + **Metformin** (**Galvus® Met** 50/500, 50/850, 50/1000 mg); ***twice*** **daily** *with* **meals**.
  - **Saxagliptin** + **Metformin XR** (**Kombiglyze® XR** 2.5/1000, 5/1000 mg); ***once*** **daily**.
  - **Linagliptin** + **Metformin** (**Jentadueto®** 2.5/500, 2.5/850, 2.5/1000 mg); ***twice*** **daily**.
  - **Linagliptin** + **Metformin XR** (**Jentadueto® XR** 2.5/1000, 5/1000); ***once*** **daily**.

Pharmaco Kinetics

- ***Absorption***;
  - **DPP-4 inhibitors** are ***well absorbed*** after **oral administration**.
  - **Food** ***does not*** *affect* the ***extent*** of **absorption**.
- ***Metabolism*** and ***Excretion***;
  - **Hepatic** ***metabolism*** of **Alogliptin**, **Sitagliptin** and **Linagliptin** are ***limited*** and ***excreted*** *mainly* **unchanged** in the **urine**.
  - **Saxagliptin** is ***metabolized*** via **CYP450 3A4/5** to an ***active*** **metabolite** (***one-half*** *as potent as* **Saxagliptin**) & ***excreted*** in **urine**.
  - **Linagliptin** is **eliminated** *via* the **feces/enterohepatic system** and ***not require*** **dosage adjustments** in **renal dysfunction**.

Mechanism OF Action

- These drugs ***inhibit*** the **DPP-4** ***enzyme***, which is ***responsible*** for the ***inactivation*** of **Incretin hormones** such as **GLP-1**.
- ***Unlike*** **Incretin Mimetics**, these drugs ***do not cause*** **satiety**, and are **weight** ***neutral***.


Incretins: GLP-1, GIP
Stimulate insulin release
Inhibit glucagon release
Lowering of blood glucose
DPP-4 enzyme inactivates incretins
DPP-4 inhibitors (drugs) block DPP-4

Side Effects

- *In general*; **DPP-4 inhibitors** are ***well tolerated***, with the ***most common*** **side effects** are **Nasopharyngitis**, **headache**, **nausea** and **hypersensitivity reactions**.
- **Post-marketing Reports** and **Warning**;
  - ***Risk*** of **acute pancreatitis** (**fatal** and **nonfatal**) and ***severe*** **allergic** and **hypersensitivity reactions** (especially with **Sitagliptin**)
  - ***Risk*** of ***severe*** and ***disabling*** **joint pain** (**Arthralgia**).
  - **Saxagliptin** and **Alogliptin** may ***increase*** the ***risk*** of **heart failure**.
  - **Vildagliptin** may cause **hepatitis** (**liver function tests** should be ***performed***).
  - **Acute liver failure** *attributed to* **Alogliptin** *have been* ***reported***.

3) *Injectable* Amylin Analogues

Pramlintide (Symlin®)

- **Pramlintide** [PRAM-lin-tide] is a ***synthetic*** **Amylin** ***analogue*** with ***substitutions*** of **Proline** at ***positions*** **25**, **28** and **29**. These modifications make **Pramlintide** ***soluble***, ***non-self*-aggregating** and *suitable for* **pharmacologic use**.
- **Pramlintide** is **used** as an ***adjunct*** to **Insulin** ***therapy*** in *patients with* **Type 1** and **Type 2 Diabetes**.
- **Pramlintide** is ***administered*** by **SC injection** ***immediately*** **prior** to **meals**;
  - When **Pramlintide** is ***initiated***, the ***dose*** of **postprandial** ***short-acting*** **Insulin** ***should be decreased by*** **50%** to ***avoid*** a ***risk*** of ***severe*** **hypoglycemia**.
- ***Dose range*** (***should be*** **initiated**); - 15 to 60 mcg SC for type 1 patients. - 60 to 120 mcg SC for type 2 patients.
- **Pramlintide** ***should*** be **injected** by **itself** ***using*** a ***separate*** **syringe**; it ***cannot*** be ***mixed with*** **Insulin**.
- **Common Side Effects**; **hypoglycemia**, **nausea**, **vomiting** and **anorexia**.
- **Contraindications**; **Hypersensitivity**, **Gastroparesis** and **Hypoglycemia** ***unawareness***.

V) Glycosurics

Sodium/Glucose Co-transporter-2 (SGLT2) Inhibitors "Gliflozins"

Dapagliflozin (Forxiga®) (Farxiga®)	**Canagliflozin** (Invokana®)
Empagliflozin (Jardiance®)	**Ertugliflozin** (Steglatro®)
Ipragliflozin (Suglat®)	**Tofogliflozin** (Apleway®)

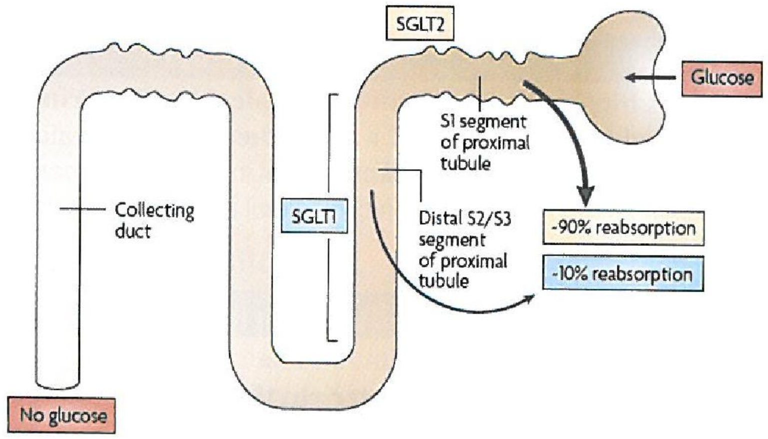
- **Dapagliflozin** [dap-a-gli-FLOE-zin] is the ***first*** **SGLT2 inhibitor** *approved in* **2011** by the **EU** (Forxiga®; for-SEE-ga) and in **2014** by **US FDA** (Farxiga®; far-SEE-ga).
- **Canagliflozin** [kan-a-gli-FLOE-zin] is the ***first*** **SGLT2 inhibitor** *approved by* **US FDA** in **2013**.
- **Empagliflozin** [em-pa-gli-FLOE-zin] is the ***third*** **SGLT2 inhibitor** *approved by* **US FDA** in **2014**.
- **Ertugliflozin** [ER-too-gli-FLOE-zin] is the ***fourth*** **SGLT2 Inhibitor** *approved in* the **US FDA** on December 19, **2017**.
- **Ipragliflozin** and **Tofogliflozin** are *approved in* **Japan**.
- **Sotagliflozin**, a ***dual*** **SGLT1/SGLT2 inhibitor**, in **phase III trials**, *under* development by Lexicon.
- ***Uses***; - As an ***adjunct*** to **diet** and **exercise** to ***improve*** **glycemic control** in **adults** with **Type 2 Diabetes**.
  - **Empagliflozin** also ***indicated*** to ***reduce*** the ***risk*** of **Cardiovascular Death** in **adults** with **Type 2 Diabetes** and **Cardiovascular Disease**.

Pharmaco Kinetics

- **SGLT2 inhibitors** are given **orally** ***once*** **daily** in the ***morning***;
  - **Canagliflozin** ***should be*** used *before* the ***first*** **meal** of the **day**.
  - **Dapagliflozin**, **Empagliflozin** and **Ertugliflozin** are **used** ***with*** or ***without*** **food** in the **morning**.
- ***Metabolism***; ***primarily*** *via* **glucuronidation**.
- ***Excretion***; **feces** and **urine**.

Mechanism OF Action

- They are ***inhibits*** **SGLT2**, which is ***responsible for*** at least **90%** of the **glucose** ***reabsorption*** in the **kidney**, ***blocking*** this **transporter** causes **blood glucose** to be ***eliminated*** *through the* **urine** → **Glycosuria**.



Side Effects

- **Renal Impairment** (>10%).
- **Urinary Tract Infection** and ***Increased*** **Urination** (<10%).
- ***Female*** **Genital Mycotic (Fungal) Infections** (<10% with **Dapagliflozin**, and **Empagliflozin**, while >10% with **Canagliflozin** and **Ertugliflozin**).
- *Others*; - ***Male*** **Genital Mycotic Infections**, **Nausea** and **Constipation**.
  - **Dyslipidemia** with **Dapagliflozin** and **Empagliflozin**.
- In **2015**, the **US FDA** issued a ***warning*** that the **SGLT2 inhibitors** may *lead to* **Ketoacidosis**.
- In **2016**, a report show the **Canagliflozin** may ↑ ***risk*** of **bone fracture**.
- In **2017**, the **FDA** *concluded* (**Boxed Warning**) that **Canagliflozin** causes an ***increased risk*** of **leg** and **foot amputations**.

Contra indication

- **Hypersensitivity** to the **drug** or ***any*** **component** of the **formulation**.
- ***Severe*** **Renal Impairment**, **End-stage Renal Disease (ESRD)** or **Patients** on **Dialysis**;
  - **Canagliflozin** and **Empagliflozin** are ***contraindicated*** in patients with estimated **GFR *less than* 45 mL/min/1.73 m²**.
  - **Dapagliflozin** and **Ertugliflozin** are ***not recommended*** for use in patients with estimated **GFR *less than* 60 mL/min/1.73 m²**.
  - **Dapagliflozin** and **Ertugliflozin** are ***contraindicated*** in ***persistent*** **GFR 30-60 mL/min/1.73 m²** or **GFR *less than* 30 mL/min/1.73 m²**.

VI) Alpha-glucosidase Inhibitors

Acarbose (Glucobay®)	**Miglitol** (Glyset®)	**Voglibose** (Voglib®)

- **Acarbose** [AY-car-bose] and **Miglitol** [MIG-li-tol] are ***available*** in the **United States**, while **Voglibose** is *available* in **Japan**, **Korea** and **India**.

Mechanism OF Action

- The **α-glucosidase inhibitors** ***competitively*** **inhibit** the ***intestinal*** **α-glucosidase enzymes**, ***delaying*** the **digestion** and **absorption** of **starch** and **disaccharides**, ***resulting*** in *lower* **postprandial glucose**.
- **Acarbose** and **Miglitol** are ***potent*** **inhibitors** of **glucoamylase**, **α-amylase**, and **sucrase** but have ***less effect*** on **isomaltase**.

Pharmaco Kinetics

- **Acarbose** is ***poorly*** **absorbed**. It is ***metabolized*** *primarily* by **intestinal bacteria**, and ***some*** of **metabolites** are ***absorbed & excreted*** in the **urine**.
- **Miglitol** is ***very well*** **absorbed** but has ***no systemic*** **effects**. It is ***excreted*** **unchanged** by the **kidney**.

Side Effects

- ***Common* Side Effects**; **flatulence**, **diarrhea** and **abdominal pain**.
- ***Contraindications***; **Patients** with **inflammatory bowel disease**, **colonic ulceration** or **intestinal obstruction**.
- **Hypoglycemia** ***should be treated*** with **Glucose** (***not*** **Sucrose**; ***breakdown*** may be **blocked**).

VII) Others

1) Bile Acid Sequestrant

Colesevelam (WelChol®)

- **Colesevelam** is **bile acid sequestrant** and **cholesterol-lowering drug**, is used in **Type 2 Diabetes** who are ***not*** **achieved *adequate* control** *with* **medications**, **diet** and **exercise**.
- The ***exact*** **mechanism** of **action** is ***unknown***, but involve in ***decrease*** **Farensoid X receptor (FXR) activation**, FXR is a nuclear receptor with effect on cholesterol and glucose metabolism.

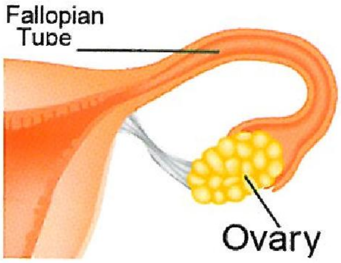
2) Dopamine Agonist

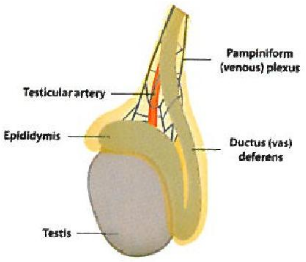
Bromocriptine (Cycloset®)

- **Quick-release** ***formulation*** of **Bromocriptine** (**Cycloset®**) given **once** in the **morning**, is believed to ***reset*** the **circadian clock** as in a **winter rhythm**; ↑ ***dopaminergic*** **neuron activity** in **morning** *lead to* ↑ **glucose tolerance**.

Gonadal Hormones and Inhibitors

- **Gonadal Hormones** (**Sex Hormones**) [**Androgens**, **Estrogens** and **Progestogens**] ***produced*** by the **gonads** are *necessary for* **conception**, **embryonic *maturation***, and ***development*** of **primary** and **secondary sexual characteristics** at ***puberty***.
- **Gonad**; is a ***mixed*** **gland** that *produces* the **Gametes** (**Sex Cells**) and **Gonadal Hormones**.
    - **Male gonad**; **Testicle**, *produces* **sperm**.
    - **Female gonad**, **Ovary**, *produces* **egg cells**.
- **Gonadal Hormones** are ***used*** **therapeutically** in **replacement therapy**, for **contraception** & in ***management*** of **menopausal symptoms**.

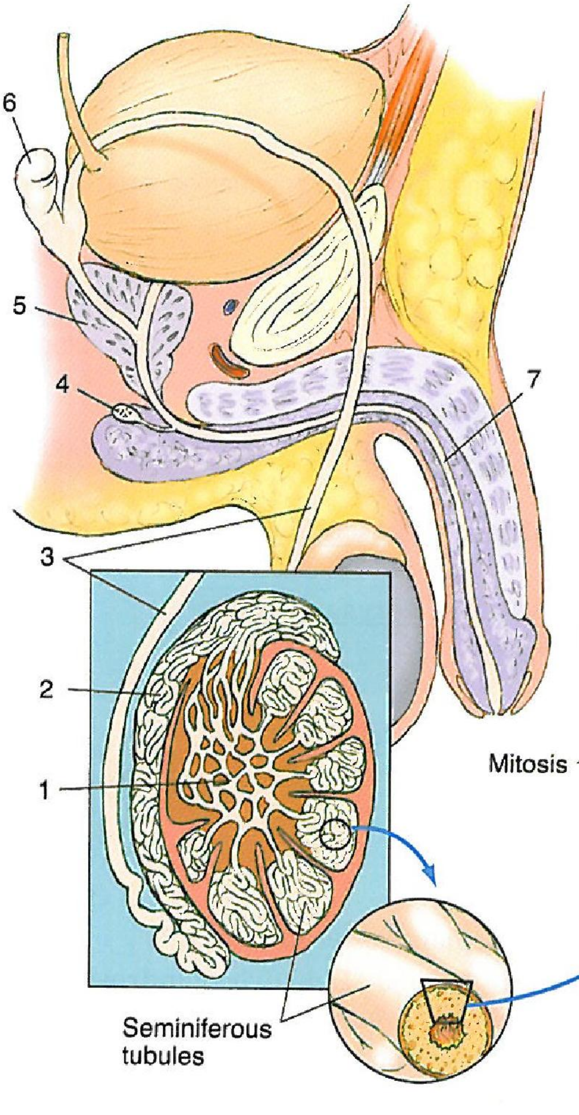

Fallopian Tube
Ovary


Pampiniform (venous) plexus
Testicular artery
Epididymis
Ductus (vas) deferens
Testis

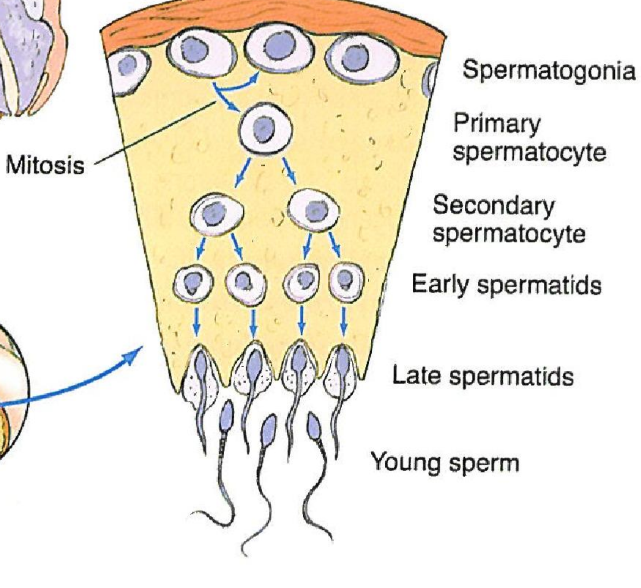
- ***Several*** **antagonists** are ***effective*** in **cancer chemotherapy**.
- ***All*** **Gonadal Hormones** are ***synthesized*** *from* the ***precursor***, **Cholesterol**, in a ***series*** of **steps**.

Testicle

- **Testicle** or **Testis** or **Testes** is the ***male*** **reproductive gland**. The ***primary*** **functions** of the **testis** are to ***produce*** **sperm** (**Spermatogenesis**) and to ***produce*** **Androgens** (primarily **Testosterone**).
- **Spermatogenesis**;


6
5
4
7
3
2
1
Seminiferous tubules

1. Testis:
   sperm develop in seminiferous tubules
2. Epididymis:
   sperm maturation and storage
3. Vas deferens:
   transport sperm during ejaculation
4. Bulbourethral gland
5. Prostate gland
6. Seminal vesicle:
   produce fluids which add nutrients, lubrication, and buffer pH
7. Urethra:
   sperm are transported in seminal fluid through the penis during ejaculation


Spermatogonia
Mitosis
Primary spermatocyte
Secondary spermatocyte
Early spermatids
Late spermatids
Young sperm

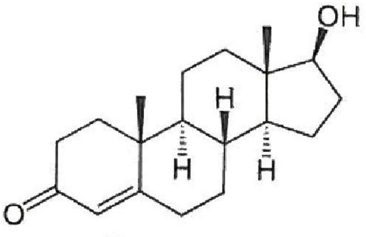
- **Factors *Affecting* Spermatogenesis**;
  - A) **Hormonal**:
    - **Follicle Stimulating Hormone (FSH)**;
      - Acts on Sertoli cells to facilitate last stage of spermatid maturation.
      - Promotes the production of androgen-binding protein (ABP); to made androgen hormones less lipophilic hormones and become high concentrated within the luminal fluid of the seminiferous tubules.
      - Stimulates Sertoli cells to convert Testosterone to Estrogen that is also required for spermatogenesis.
      - Sensitizes Leydig cells to LH action.
    - **Luteinizing Hormone (LH)**;
      - Stimulate Leydig cells to produce testosterone to maintaining spermatogenesis.
    - **Androgens**;
      - Spermatogenesis (early stage).
      - Complete meiosis.
      - Development of the germinal epithelium (wall of the seminiferous tubule within the testes)
    - **Inhibin** and **Activin**;
      - Activin; enhances FSH synthesis and secretion.
      - Inhibin; inhibits FSH synthesis and secretion.
    - **Thyroid Hormones**, **Growth Hormone** and **Prolactin**;
      - They are having important role in male reproductive functions and spermatogenesis.
  - B) ***Non*-hormonal**:
    - **Temperature**;
      - The testes are located outside the body in the scrotum.
      - Prolonged fevers, hot baths and tight clothes can inhibit spermatogenesis.
    - **Other Factors**;
      - Vitamins A, B, C and E are vital for spermatogenesis.
      - Anabolic steroids, oxidative stress, metals (cadmium & lead), x-ray exposure, dioxin, alcohol, infectious diseases & pesticides will also adversely affect the rate of spermatogenesis.

Androgens

- **Androgens** are a ***group*** of **steroids** that have **anabolic** and/or **masculinizing effects** in ***both*** **males** and **females**.
- **Androgens** are ***synthesized*** in the **testes**, the **ovaries** and the **adrenal glands**;
  - Males produce 20 times more testosterone than Females.
  - Females are also more sensitive to the hormone.
- The ***most*** **important androgen** *secreted by* the **testes** is **Testosterone**;
  - The pathways of synthesis of testosterone in the testes are similar to those previously described for the adrenal gland (Steroidogenesis; page no. 909).
- The **testes** also ***secretes*** **small amounts** of;
  - ***Potent*** **androgen**; **Dihydrotestosterone (DHT)**.
  - ***Weak*** **androgens**; **Androstenedione** and **Dehydroepiandrosterone (DHEA)**.
- **Androstenedione**, **Dehydroepiandrosterone (DHEA)** and **Dehydroepiandrosterone Sulfate (DHEAS)** are **largely *produced*** in the **adrenal gland *rather than*** in the **testes**.
  - DHEA supplements may help people with; depression, obesity, lupus, and adrenal insufficiency.
  - DHEA supplements may also improve skin in older people and help treat osteoporosis, vaginal atrophy, erectile dysfunction and some psychological conditions.

Testosterone

- **Testosterone** [tess-TOSS-terone], the ***most important*** **androgen** in humans, is *synthesized by*;
  - **Leydig cells** in the **testes** in ***male***.
  - **Thecal cells** in the **ovaries** in ***female*** (small amounts).
  - **Adrenal glands** in ***both*** **sexes**.
- In **men**, *approximately* **8 mg** of **Testosterone** is *produced* **daily**;
  - *About* **95%** is *produced by* the **Leydig cells**.
  - ***Only*** **5%** by the **adrenals**.



Testosterone

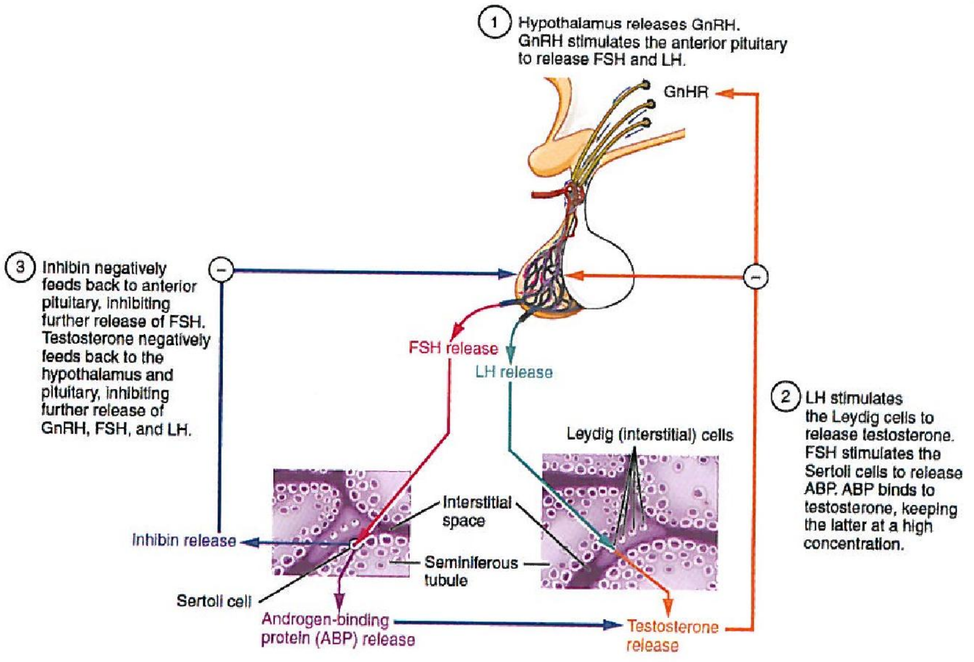
Normal Values

- ***Male*** (after puberty); 280–1100 ng/dL = 0.28-1.1 mcg/dL (decline after age 50).
- ***Female***; 15–70 ng/dL = 0.015-0.07 mcg/dL.

Pharmaco Kinetics

- ***Distribution*** (**Plasma Protein Binding**);
  - *About* **65%** of *circulating* **Testosterone** is *bound to* **Sex Hormone-binding Globulin (SHBG)**.
    - **SHBG** is ***increased*** by; **Estrogen**, **thyroid hormone** and in ***patients*** with **liver cirrhosis**.
    - **SHBG** is ***decreased*** by; **Androgen**, **growth hormone** and in **obese** *individuals*.
  - *About* **33%** is *bound to* **Albumin**.
  - *Only* **2%** ***remains*** **free** and ***available*** to ***enter*** **cells** and ***bind*** to **intracellular receptors**.
- ***Metabolism***;
  - ***Many*** **target tissues**;
    - **Testosterone** is ***converted to*** **Dihydrotestosterone (DHT)** *by* **5α-reductase** ***enzyme***.
  - ***Some*** **tissues** (including; adipose tissue, liver and hypothalamus);
    - **Testosterone** is ***converted to*** **Estradiol** *by* **P450 aromatase** ***enzyme*** **(aromatization)**.
- ***Degradation*** and ***Excretion***;
  - *Finally*, ***Most*** of the **Testosterone** and **DHT** ***deactivated*** by **enzymes** and ***converted to inactive*** **substances**.
  - ***Inactive*** **substances** are ***conjugated*** and *then* ***excreted*** in **urine**.

Regulation



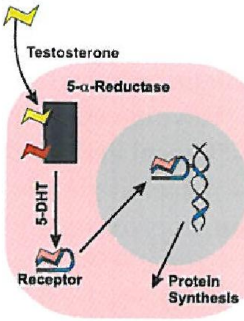
① Hypothalamus releases GnRH. GnRH stimulates the anterior pituitary to release FSH and LH.

② LH stimulates the Leydig cells to release testosterone. FSH stimulates the Sertoli cells to release ABP. ABP binds to testosterone, keeping the latter at a high concentration.

③ Inhibin negatively feeds back to anterior pituitary, inhibiting further release of FSH. Testosterone negatively feeds back to the hypothalamus and pituitary, inhibiting further release of GnRH, FSH, and LH.

Mechanism OF Action

- *Like other* **steroids**, **Testosterone** ***acts*** **intracellularly** in **target cells**, it is ***converted to*** **5α-dihydrotestosterone** by **5α-reductase**.
- **Testosterone** and **Dihydrotestosterone** ***bind*** to the ***intracellular*** **androgen receptor**, *initiating* a ***series*** of **events**, *leading to* ***growth***, ***differentiation***, and ***synthesis*** of a *variety of* **enzymes** and other *functional* **proteins**.



Function

A) Androgenic Effects

1) ***During*** **Intrauterine Life**;
   - ***Development*** of ***external*** **male genitalia**.
   - ***Descent*** of the **testicles** in the **scrotum**.
2) ***During*** **Puberty** and **Adult** (**Masculinizing Effects**);
   - ***Primary*** **Sex Organs** (Testes):
     - ***Essential*** for **spermatogenesis**.
   - ***Secondary*** **Sex Organs** (*other than* Testes);
     - ***Development*** and ***growth*** of ***external*** **genitalia**.
     - ***Growth*** and *maintain* ***functions*** of **seminal vesicles** and **prostate**.
   - ***Secondary*** **Sex Characteristics**;
     - **Skin**; ↑ **sebaceous gland** ***secretion*** → **Acne**.
     - **Hair**; ↑ **hair** in **pubic**, **beard**, **chest**, **axillary** and ***general*** **body hair**.
     - **Voice**; ***become*** **deeper**.
     - **Libido**; ↑ **Libido** in **males** and **females**.

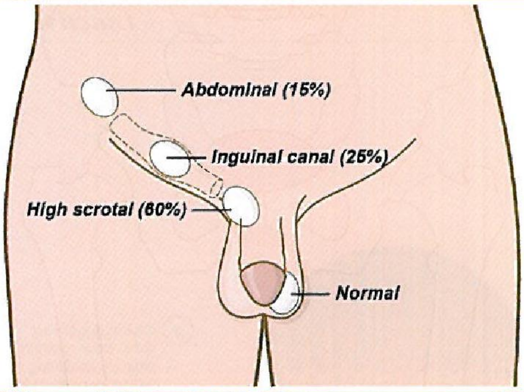
B) Anabolic Effects

- **Muscle**; ***Increase*** **growth** of **muscle mass** and **strength**.
- **Bone**; - ***Increase*** **bone density** and **strength**.
  - ***Stimulation*** of **linear growth** and **bone maturation**.

Disturbance of Testosterone Hormone Functions

Cryptorchidism

- **Cryptorchidism** is the ***absence*** of **one** or ***both*** **testes** *from the* **scrotum**.
- *Overall*, **3%** of ***full-term*** **male** ***newborns*** (*About* **30%** of **premature infant boys**) have **cryptorchidism**, ***decreasing*** to **1%** in **male infants** ***aged*** **6 months** to **1 year**.
- **Cryptorchidism** ***should be*** **treated** when the **patient** is *approximately* **6 months old**.
- ***Primary*** **hormonal therapy** with **Human Chorionic Gonadotropin** (**hCG**), ***ranging from*** **3-15 doses**.



Congenital 5α-reductase Deficiency (5-ARD)

- *Many* **patients** with **5α-reductase Deficiency** are ***born*** with ***external*** **genitalia** that ***appear*** **female**.
- In *other cases*, the **external genitalia** ***do not*** **look** ***clearly*** **male** or ***clearly*** **female** (ambiguous genitalia).

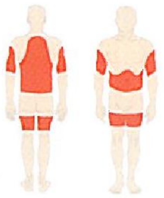
Male Hypogonadism

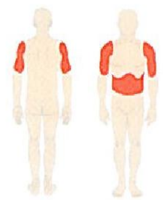
- **Male** ***primary*** **hypogonadism** is a **condition** in which the **testicles** ***doesn't*** **produce** ***enough*** **Testosterone** (secondary hypogonadism; hypothalamic-pituitary origin).
- **Hypogonadism** can begin ***during*** **fetal development**, ***before*** **puberty** or ***during*** **adulthood**. **Signs** and **symptoms** ***depend on*** **when** the **condition** ***develops***.

Androgenic/Anabolic Steroid (AAS) Preparations

- **Testosterone** (AndroGel®) (Androderm®)
- **Testosterone Undecanoate** (Andriol®)
- **Testosterone Propionate** (Testoviron®)
- **Testosterone Cypionate** (Depo-Testosterone®)
- **Testosterone Enanthate** (Cidotestone®) (Delatestryl®)
- **Methyltestosterone** (Testred®)
- **Fluoxymesterone** (Halotestin®)
- **Oxymetholone** (Anadrol®)
- **Oxandrolone** (Oxandrin®)
- **Metenolone** (Primobolan®)
- **Methandienone** (Dianabol®)
- **Stanozolol** (Winstrol®)
- **Mesterolone** (Proviron®) (Cidoviron®)
- **Nandrolone Decanoate** (Deca-Durabolin®)

- **Anabolic–androgenic Steroids** (**AAS**) are ***steroidal*** **androgens** that *include* ***natural*** or ***synthetic*** **androgens** that are **structurally *related*** and have ***similar*** **effects** to **Testosterone**.
- ***Orally*** **administration** of **Testosterone** is ***rapidly*** **absorbed**, *but* it is ***largely*** *converted to* ***inactive*** **metabolites**; ***Alkylation*** of **Testosterone** at the **17α position** *such as* **Methyltestosterone**, **Fluoxymesterone** and **Oxymetholone** *allows* ***oral*** **administration** of the **hormone**.
- **Androgenic-*to*-anabolic Ratio**;
  - **Testosterone**; 1:1
  - **Methyltestosterone**; 1:1
  - **Oxandrolone**; 1:3 to 1:13
  - **Testosterone Cypionate**; 1:1
  - **Oxymetholone**; 1:3
  - **Nandrolone Decanoate**; 1:2.5 to 1:4
  - **Testosterone Enanthate**; 1:1
  - **Fluoxymesterone**; 1:2
- ***Routes*** of ***administration***;
  - **Oral**; *such as* **Methyltestosterone**, **Fluoxymesterone**, **Oxymetholone**, **Mesterolone** and **Oxandrolone**.
  - **IM Injections**; *such as* **Testosterone *esters*** (**Enanthate**, **Undecanoate**, or **Cypionate**) & **Nandrolone Decanoate**.
  - **Creams/Gels** or **Skin Patches**; **Testosterone**;
    - DO NOT APPLY TO THE SCROTUM (application sites)→
      - Scrotal skin is ~ 5 times more permeable to testosterone.


Testosterone patches (Androderm®)


Testosterone gel (AndroGel®)

Therapeutic Uses

- *Since* the ***discovery*** and ***synthesis*** of **Testosterone** in the **1930s**, **AAS** have been ***used*** *as*;

A) **Androgenic**;
- **Androgen Replacement Therapy**; *Only* for men with low levels of testosterone (hypogonadal men).
- ***Induction*** of **Male Puberty**; to increase height, weight, and fat-free mass in boys with delayed puberty.
- **Masculinizing Hormone Therapy**; to induce masculine secondary sexual characteristics in transgender (female-to-male).

B) **Anabolic**;
- **Bone Marrow Stimulation**: *especially* **aplastic anemia**; AAS have largely been replaced in this setting by synthetic human erythropoietin.
- **Growth stimulation**: especially people with chronic wasting conditions such as cancer and AIDS.
- **Osteoporosis** in **postmenopausal women**; Nandrolone Decanoate is approved for this use.
- **Aging males**; increase in lean body mass and a decrease in bone turnover.

C) **Ergogenic** [illicit use] (abuse in sports);
- Uses of AAS in sports, racing, and bodybuilding as performance-enhancing drugs are controversial because of their adverse effects and the potential to gain unfair advantage in physical competitions.
- In the adult male, large doses of testosterone—when given alone—or its derivatives suppress the secretion of gonadotropins and result in some atrophy of the interstitial tissue and the tubules of the testes.

D) **Others**;
- **Breast Cancer** in ***women***.
- **Postmenopausal** and **Transgender Women**; ↑ libido and quality of life.
- **Postpartum**; reduce breast engorgement.

Side Effects

- **Male**-*specific*; **priapism, gynecomastia, azoospermia, testicular** *atrophy*, **prostate hypertrophy** and **prostate cancer**.
- **Female**-*specific*: **masculinization, voice deepening, hirsutism, menstrual** *disturbances*, **clitoral** *enlargement*, **breast atrophy** and **uterine atrophy**.
  - Testosterone *should not* be used by **pregnant women** because of *possible* **virilization** of the **female fetus**.
- **Child**-*specific*: *premature* **epiphyseal closure** (short stature), **precocious puberty** in *boys*, **delayed puberty** and *contra-sexual* **precocity** in *girls*.
- **General**;
  - *Dermatological*; **oily skin, acne, stretch marks** (rapid muscle enlargement), **hypertrichosis** (excessive body hair growth), **androgenic alopecia** and **fluid retention/edema**.
  - *Endocrine*: **libido** *changes*, **infertility** and **hypogonadism**.
  - *Hepatic*: *elevated* **liver function tests** and **hepatotoxicity**; *exclusively with* **17α-alkylated AAS** *such as* **Methyltestosterone**, **Oxymetholone**.
  - *Cardiovascular*: **dyslipidemia** (increased LDL levels and decreased HDL levels), **atherosclerosis, hypertension** (sodium and water retention) **thrombosis, myocardial infarction** and *sudden* **death**.
  - *Psychiatric*; **mood** *swings*, **anxiety** and **cognitive** *impairment*.

Antiandrogens

Androgen Receptor (AR) Antagonists

Flutamide (Eulexin®) | Nilutamide (Nilandron®) | Bicalutamide (Casodex®)

Enzalutamide (Xtandi®) | Apalutamide (Erleada®)

- **Flutamide** [FLOO-ta-mide], **Nilutamide** [ni-LOO-ta-mide], **Bicalutamide** [bye-ka-LOO-ta-mide] are *first generation* **non-steroidal antiandrogen** (**NSAAs**), *while* **Enzalutamide** [en-za-LOO-ta-mide] and **Apalutamide** [a-pa-LOO-ta-mide] (Apalutamide was approved in February 2018) are *second generation* **non-steroidal antiandrogen** (**NSAAs**); ↑ efficacy and potency and shows less side effects.
- **NSAAs** are *used* for the **treatment** *of* **Prostate Cancer**.

Cyproterone Acetate (Androcur®) (Diane® 35)

- **Cyproterone acetate** (Androcur®) or *with* **Ethinylestraidol** (Diane® 35), is an ***antiandrogen*** with ***progestational effect*** (suppresses the feedback enhancement of LH and FSH, leading to a more effective antiandrogen effect), which is *used* in the *treatment* of **androgen-dependent conditions** *like* **acne, seborrhea, hirsutism, early puberty, prostate cancer** and in **birth control**

Spironolactone (Aldactone®)

- **Spironolactone** [speer-on-oh-LAK-tone] is a *synthetic* **steroid** that *acts as* a **competitive antagonist** at **mineralocorticoid receptors** and **androgen receptors**, which is *used* in the *treatment* of **androgen-dependent conditions**; **hirsutism, acne** in *women* and **androgenic alopecia**.

Androgen Synthesis Inhibitors

Ketoconazole | Abiraterone (Zytiga®)

- **Ketoconazole** [kee-toe-KOE-na-zole] is an **antifungal** and *older* **17α-hydroxylase** *inhibitor*.
- **Abiraterone** [A bir A te rone] is a *new* **17α-hydroxylase** *inhibitor*, *used* in **Prostate Cancer**.

Finasteride (Proscar®) | Dutasteride (Avodart®) | Alfatradiol (Pantostin®)

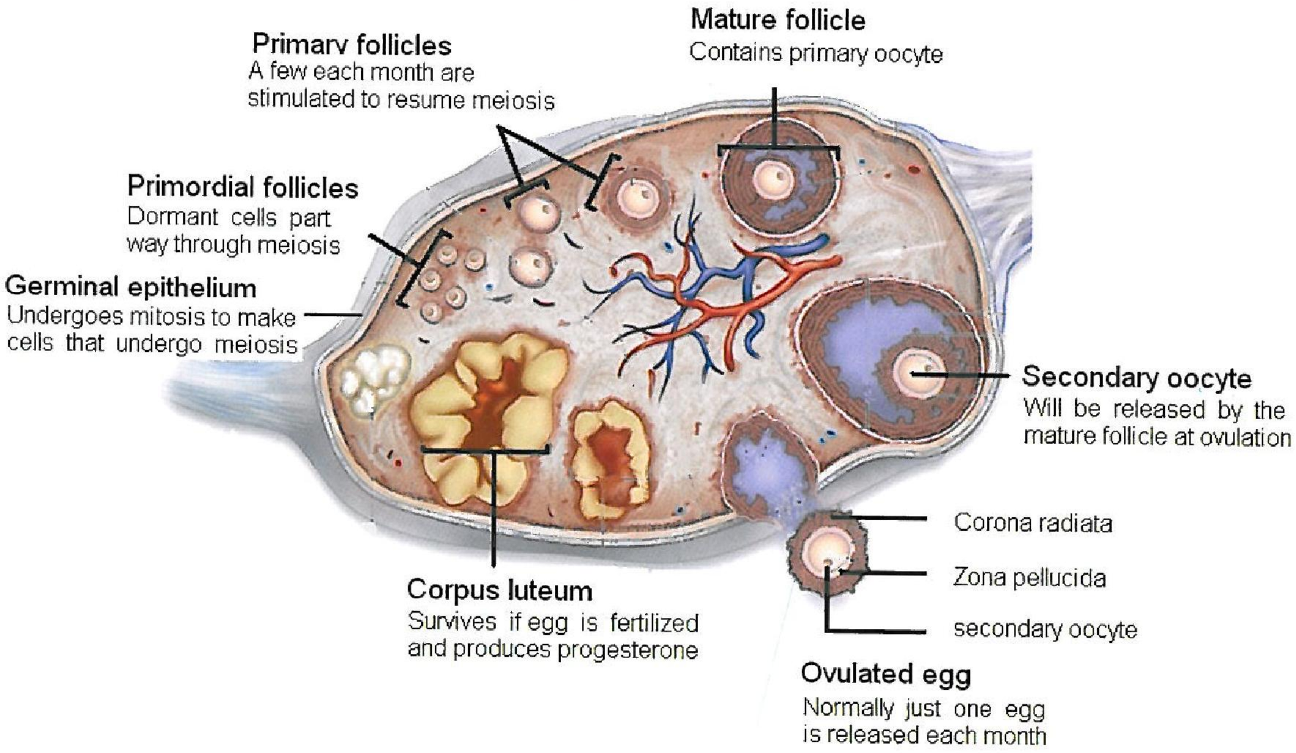
- **Finasteride** [fin-AS-ter-ide] and **Dutasteride** [doo-TAS-teer-ide] are **5α-reductase** ***inhibitors***, they are *used* in **Benign Prostatic Hyperplasia (BPH)**.
- **Finasteride** is *also* **used** in **Androgenic Alopecia** and **Hirsutism**.
- **Alfatradiol** is *another* ***5α-reductase inhibitor*** **used** ***topically*** in **Androgenic Alopecia**.

Gossypol

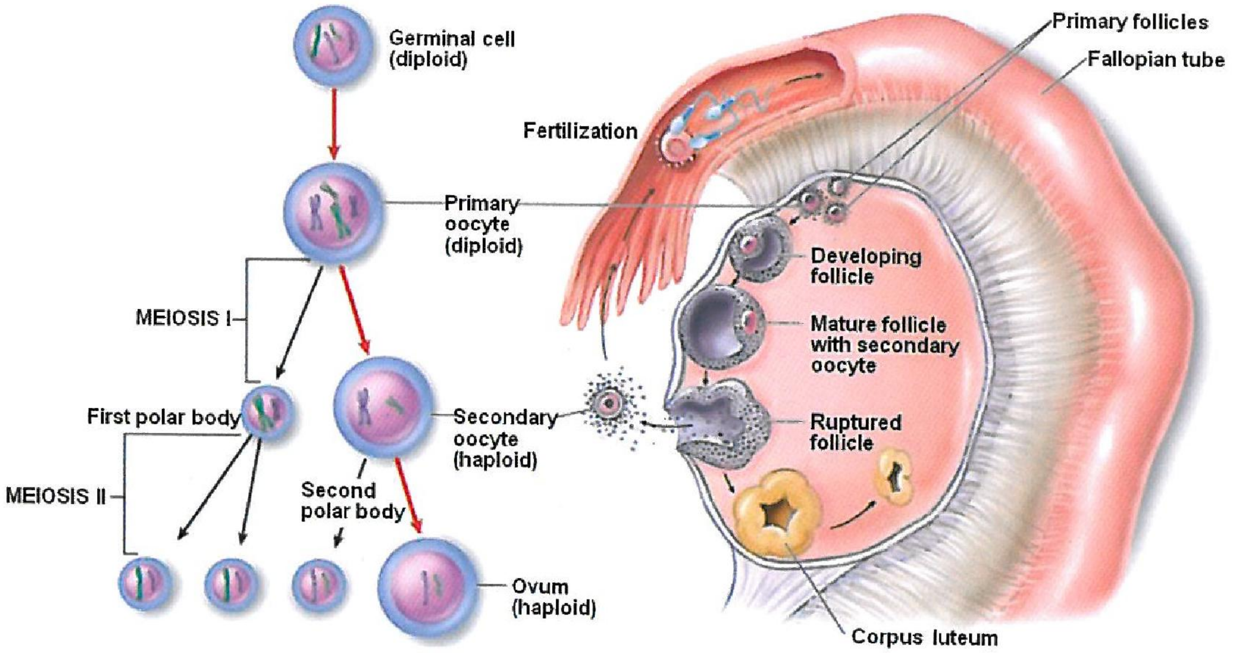
- In the 1970s, the Chinese government began researching the use of gossypol (cottonseed) as male oral contraceptive. In 1986, the Chinese stopped research because of these side effects.

Ovary

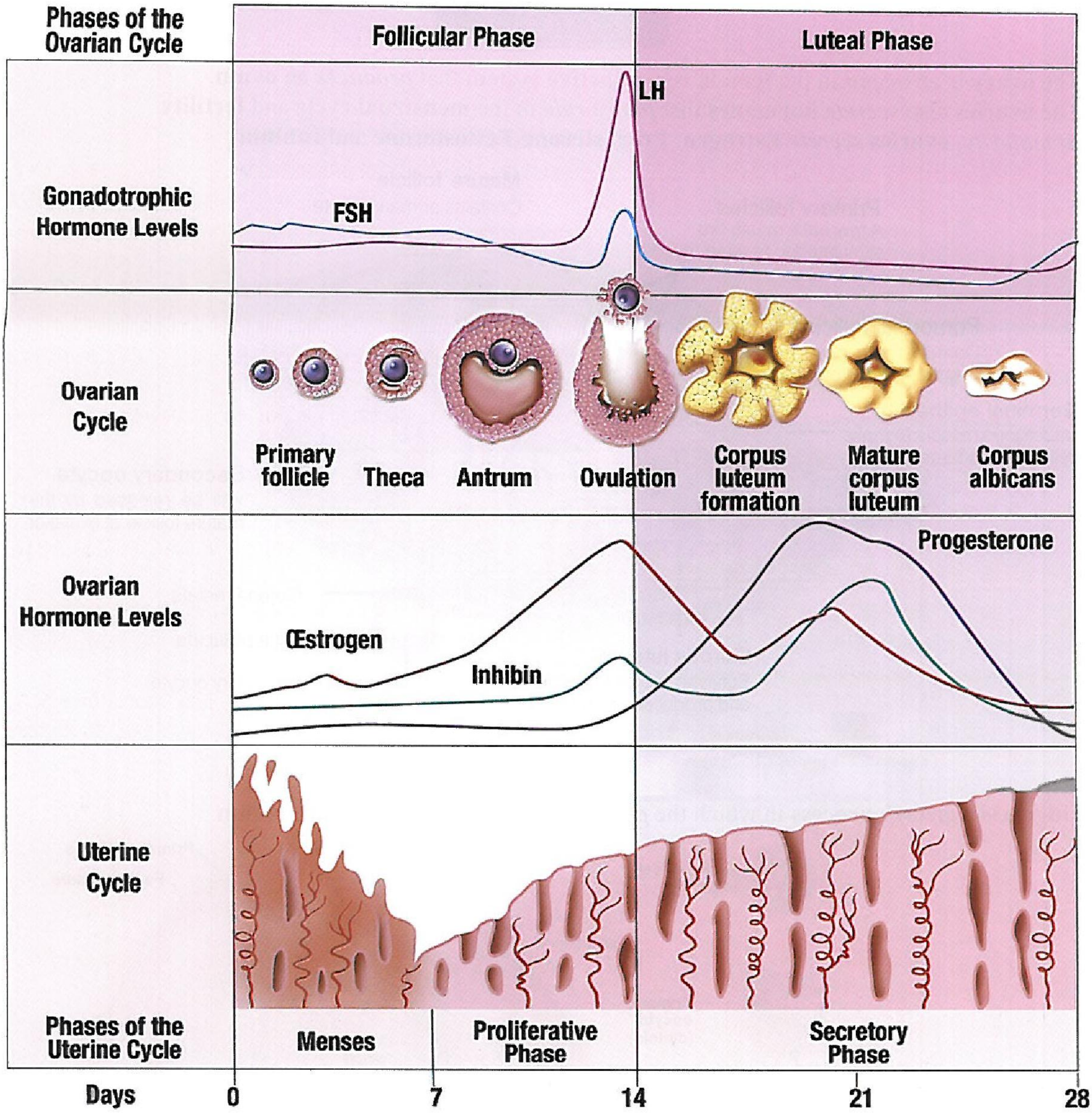
- The **ovary** is an ***organ*** in the **female reproductive system** that ***produces*** an **ovum.**
- The **ovaries** also ***secrete*** **hormones** that ***play*** a ***role*** in the **menstrual cycle** and **fertility**.
- *At maturity*, **ovaries** ***secrete*** **Estrogen**, **Progesterone Testosterone** and **Inhibin**.


Mature follicle
Contains primary oocyte
Primarv follicles
A few each month are stimulated to resume meiosis
Primordial follicles
Dormant cells part way through meiosis
Germinal epithelium
Undergoes mitosis to make cells that undergo meiosis
Secondary oocyte
Will be released by the mature follicle at ovulation
Corona radiata
Zona pellucida
secondary oocyte
Corpus luteum
Survives if egg is fertilized and produces progesterone
Ovulated egg
Normally just one egg is released each month

- **Oogenesis**; ***growth*** **process** in which the ***primary*** **oocyte** *becomes* a ***mature*** **ovum**.


Germinal cell (diploid)
Primary oocyte (diploid)
MEIOSIS I
First polar body
Secondary oocyte (haploid)
MEIOSIS II
Second polar body
Ovum (haploid)
Fertilization
Primary follicles
Fallopian tube
Developing follicle
Mature follicle with secondary oocyte
Ruptured follicle
Corpus luteum

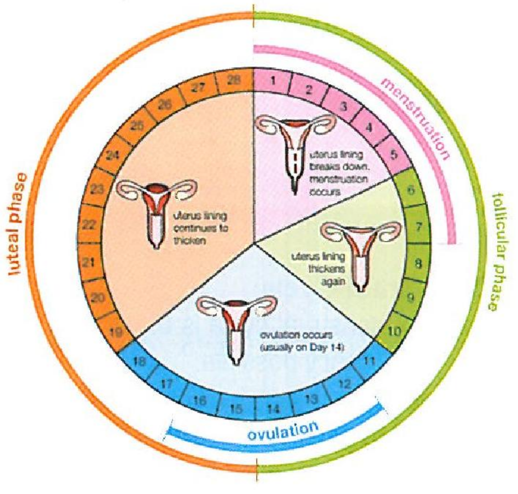
- **Menstrual Cycle**;
  - The menstrual cycle is the regular natural change that occurs in the female reproductive system that makes pregnancy possible.
  - The cycle is required for the production of oocytes, and for the preparation of the uterus for pregnancy.
  - Menstruation stops occurring after menopause which usually occurs between 45 and 55 years of age.
  - The average menstrual cycle lasts 28 days. The variability of menstrual cycle lengths is highest for women under 25 years of age and is lowest, that is, most regular, for ages 25 to 39.
  - The different phases of the menstrual cycle correlate with women's moods.


Phases of the Ovarian Cycle
Follicular Phase
Luteal Phase
Gonadotrophic Hormone Levels
LH
FSH
Ovarian Cycle
Primary follicle
Theca
Antrum
Ovulation
Corpus luteum formation
Mature corpus luteum
Corpus albicans
Ovarian Hormone Levels
Progesterone
Œstrogen
Inhibin
Uterine Cycle
Phases of the Uterine Cycle
Menses
Proliferative Phase
Secretory Phase
Days
0
7
14
21
28

A) Ovarian Cycle;

1) Follicular Phase;

- The follicular phase is the first part of the ovarian cycle.
- The body prepares itself to accept and support a pregnancy.
- The endometrium (lining of the uterus) grows and thickens, and the vaginal environment also changes in order to become more sperm friendly.
- During this phase; increase secretion of FSH during the first days of the cycle to stimulate ovarian follicles, of which one becomes dominant before ovulation.
- The follicle that reaches maturity is called a Graafian and it contains the ovum.
- Two hormones dominating the follicular phase are FSH and Estrogen.


menstruation
follicular phase
ovulation
luteal phase
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
uterus lining breaks down, menstruation occurs
uterus lining thickens again
ovulation occurs (usually on Day 14)
uterus lining continues to thicken

2) Ovulation Phase;

- Ovulation is the second phase of the ovarian cycle.
- Each cycle, only one egg is released from the dominant ovarian follicle in response to a surge in LH, and can only be fertilized for up to 48 hours.

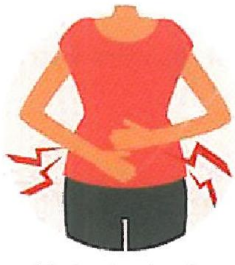
3) Luteal Phase;

- The luteal phase is the final phase of the ovarian cycle.
- During the luteal phase, corpus luteum produce high levels of progesterone and moderate levels of estrogen and inhibin.
- The hormones produced by the corpus luteum also suppress production of the FSH and LH that the corpus luteum needs to maintain itself.
- Glands in the endometrium secrete proteins in preparation for the implantation of the fertilized egg.
  - If pregnant, the embryo will implant itself in the endometrium during this phase.
  - If implantation does not occur, the endometrium starts to break down and is eventually sloughed off menstruation.
- Falling levels of progesterone trigger menstruation and the beginning of the next cycle.

B) Uterine Cycle;

1) Menses Phase;

- Menses or menstrual bleeding is the first phase of the uterine cycle.
- Regular menstruation that lasts for a few days (usually 3 to 5 days, but anywhere from 2 to 7 days is considered normal).
- The average blood loss during menstruation is 35 milliliters with 10–80 ml considered normal.
- Painful cramping in the abdomen, back, or upper thighs is common during the first few days of menstruation.
- Severe uterine pain during menstruation is known as **dysmenorrhea**, and it is most common among adolescents and younger women, Common symptoms include abdominal pain, breast tenderness and swelling, headache and back pain.



Abdominal pain

Breast tenderness

Headache

Back pain

- **Premenstrual Syndrome (PMS)** is a combination of emotional, physical, psychological, and mood disturbances that occur in the one to two weeks before Menstruation; Common symptoms include acne, breast tenderness, bloating, feeling tired, irritability and mood changes.

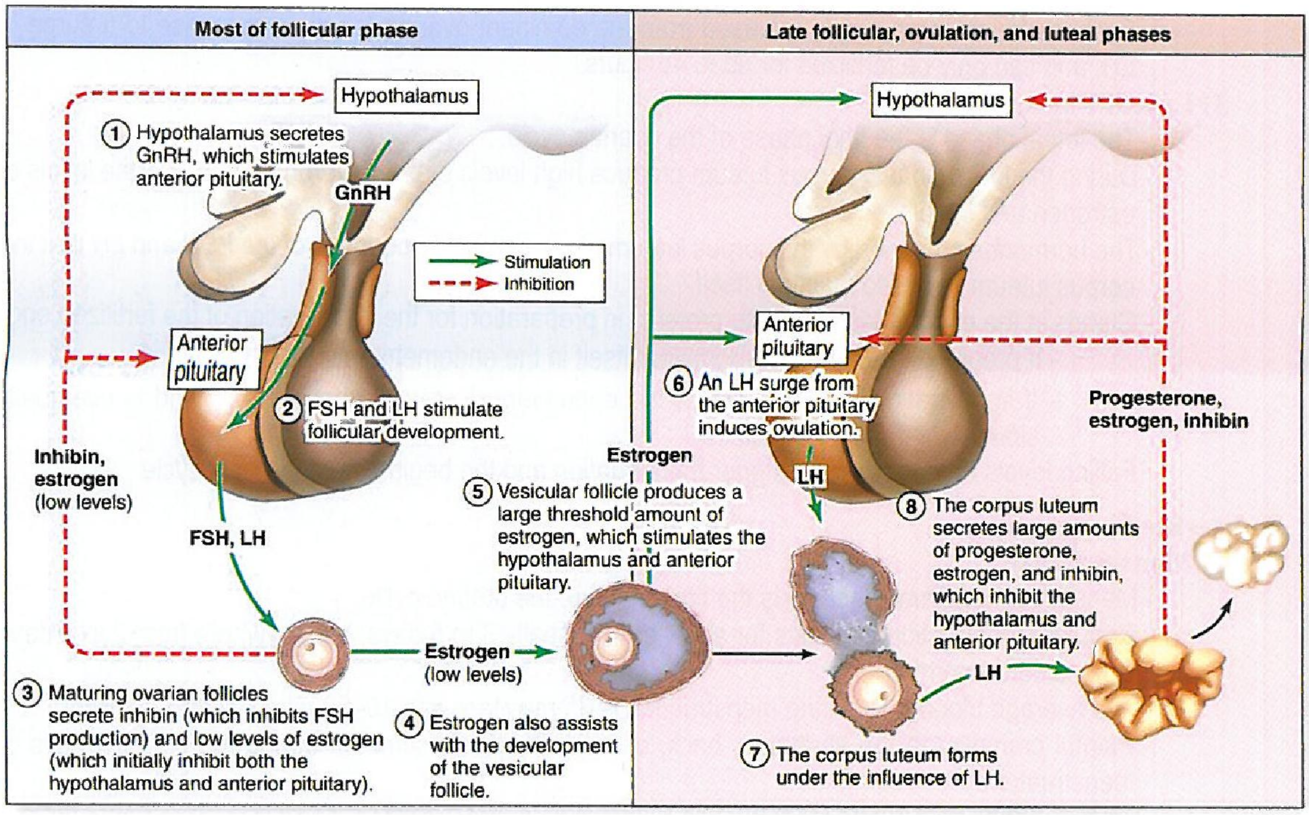
2) Proliferative Phase;

- The proliferative phase is the second phase of the uterine cycle when estrogen causes the lining of the uterus to grow, or proliferate, during this time.
- The ovarian follicles secrete increasing amounts of estradiol (estrogen).
- The estrogens initiate the formation of a new layer of endometrium in the uterus, histologically identified as the proliferative endometrium.
- The estrogen also stimulates crypts in the cervix to produce fertile cervical mucus, which may be noticed by women practicing fertility awareness.

3) Secretory Phase;

- The secretory phase is the final phase of the uterine cycle.
- The corpus luteum produces progesterone, which plays a vital role in;
  - Making the endometrium receptive to implantation.
  - Supportive of the early pregnancy, by increase blood flow and uterine secretions and reducing the contractility of the smooth muscle in the uterus.
  - It also has the side effect of raising the woman's basal body temperature (BBT).

- **Regulation** *of the* **Ovarian Cycle**;


Most of follicular phase
Late follicular, ovulation, and luteal phases
Hypothalamus
① Hypothalamus secretes GnRH, which stimulates anterior pituitary.
GnRH
Stimulation
Inhibition
Anterior pituitary
② FSH and LH stimulate follicular development.
Inhibin, estrogen (low levels)
FSH, LH
③ Maturing ovarian follicles secrete inhibin (which inhibits FSH production) and low levels of estrogen (which initially inhibit both the hypothalamus and anterior pituitary).
Estrogen (low levels)
④ Estrogen also assists with the development of the vesicular follicle.
Estrogen
⑤ Vesicular follicle produces a large threshold amount of estrogen, which stimulates the hypothalamus and anterior pituitary.
Hypothalamus
Anterior pituitary
⑥ An LH surge from the anterior pituitary induces ovulation.
LH
Progesterone, estrogen, inhibin
⑧ The corpus luteum secretes large amounts of progesterone, estrogen, and inhibin, which inhibit the hypothalamus and anterior pituitary.
LH
⑦ The corpus luteum forms under the influence of LH.

Estrogens

- The *major* **Estrogens** *produced by* **women** are **Estrone** (E_1), **Estradiol** (E_2) and **Estriol** (E_3). ***Another type*** called **Estetrol** (E_4) is *produced only during* **pregnancy**.
- **Estradiol** (E_2) is the ***major*** **secretory *product*** of the **ovary**.
- **Estradiol** (E_2) is the ***strongest***, *whereas* **Estriol** (E_3) is the ***weakest***.
- **Estrogens**, in females, are ***produced*** *primarily* by the **ovaries** and **placenta** (during pregnancy) *under the **effect*** of **FSH**.
- ***Some*** **Estrogens** are also **produced** in ***smaller amounts*** by **other tissues** *such as* **liver**, **adrenal glands**, **adipose tissue** and **breasts**.

Estrone (E_1)	Estradiol (E_2)	Estriol (E_3)	Estetrol (E_4)

- **Estradiol** [ess-tra-DYE-ole] (**17β-estradiol**) is the ***most potent*** **estrogen** *produced* and *secreted by* the **ovary**. It is the ***principal*** **estrogen** in **premenopausal women**.
- **Estrone** [ESS-trone] and **Estriol** [ess-TRI-ole] are a ***metabolite*** of **Estradiol**
- **Estrone** is the ***primary*** *circulating* **estrogen** ***after*** **menopause** and it is ***generated*** *mainly* from *conversion of* **Androstenedione** in ***peripheral*** **tissues**.

Normal Values

- ***Reference*** **Ranges** of **Estradiol *Levels*** in **Adults**;
  - **Male**; 10-40 pg/mL.
  - ***Premenopausal*** **Female**;

Mid-follicular	Periovulatory	Mid-luteal
27-123 pg/mL	96-436 pg/mL	49-294 pg/mL

  - ***Postmenopausal*** **Female**; < 10 pg/mL
- ***Reference*** **Ranges** of **Estrone *Levels*** in **Adults**;
  - **Male**; 10-60 pg/mL.
  - ***Premenopausal*** **Female**;

Mid-follicular	Periovulatory	Mid-luteal
30-100 pg/ml	> 150 pg/ml	90–160 pg/ml

  - ***Postmenopausal*** **Female**; < 40 pg/mL.

Pharmaco Kinetics

- ***Distribution*** (**Plasma Protein Binding**);
  - **Estrogens** are ***bound*** to **Sex Hormone-binding Globulin** (**SHBG**) and **Albumin**.
- ***Metabolism***;
  - **Estrogens** are ***metabolized*** *via* **hydroxylation** by **CYP450 enzymes** and *via* **conjugation**.
  - **Estradiol** is ***converted*** by the **liver** and ***other*** **tissues** to **Estrone** and **Estriol**.
- ***Excretion***;
  - **Estrogens** are ***excreted*** *primarily* by **kidneys** as ***conjugates*** *via* **urine**.
  - ***Some*** of the **water-soluble conjugates** are ***excreted*** *via* the **bile duct**, and **partly** ***reabsorbed*** *after* **hydrolysis** from the **intestinal tract**, the ***resulting*** **enterohepatic circulation** and ***contributes*** to *maintaining* **Estradiol** ***levels*** (to avoid hepatic effects of estrogen, avoid routes that have first-pass effects).
  - **Estrogens** are also ***excreted*** in ***small*** **amounts** in the **breast milk** of **nursing mothers**.

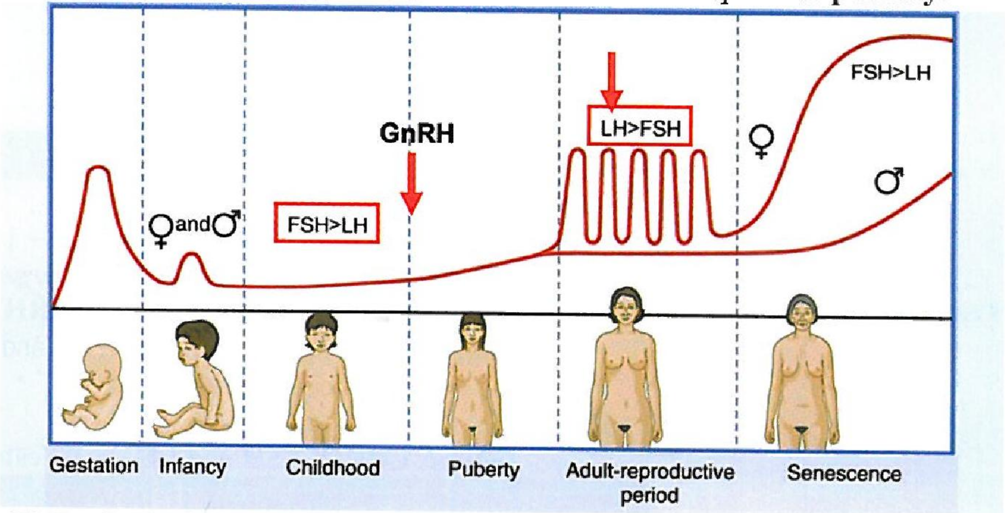
Mechanism OF Action

- *Like* ***all*** **Steroid Hormones**, **Estrogens** ***readily*** **diffuse** *across* the **cell membrane**. Once ***inside*** the **cell**, they **bind** to and ***activate*** **estrogen receptors** (ERα and ERβ) to *form* **receptor-hormone complex**.
- The **receptor-hormone complex** bind to a ***specific*** **sequence** of **nucleotides**, called **estrogen response elements** (**EREs**), which in *turn* ***modulate*** the **expression** of ***many*** **genes**.

Function

Female Reproductive System

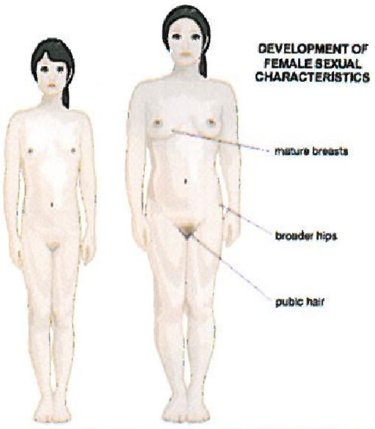
1) ***During*** **Intrauterine Life**;
   - ***Development*** of the **female sexual organs** (uterus and vagina).
2) ***Before*** **Puberty**;
   - ***Low*** **Estrogen** *levels* → ***inhibits*** **GnRH** ***release*** *prior to* **puberty**.



3) ***During/After*** **Puberty**;
   - ***Primary*** **Sex Organs** (ovary):
     - ***Facilitate*** **growth** of ***immature*** **ovarian follicles**.
     - ***Surge*** in **Estrogen** level ***induces surge*** of **LH** → *essential for* **ovulation** and **corpus luteum** ***formation***.
   - ***Secondary*** **Sex Organs** (*other than* ovary);
     - **Uterus**;
       - **Endometrium** → ↑ ***proliferation*** and ***growth***.
       - **Myometrium** → ↑ ***proliferation*** & ↑ ***sensitivity*** to **Oxytocin**.
         - Estrogen together with progesterone promotes and maintains the uterus lining in preparation for implantation of fertilized egg and maintenance of uterus function during gestation period.

- **Cervix**; ↑ ***secretion*** of **thin alkaline mucus** → ***promote*** **sperm transport.**
- **Vagina**; - ***Increase*** **vaginal lubrication.**
  - ***Thicken*** the **vaginal wall.**
    - **Epithelial *proliferation*** and ***cornification*** (more resistant to ulcerations from infection or trauma).
- **Fallopian Tubes**; ***Increase*** **activity** on **tubal motility.**

- *Secondary* **Sex Characteristics**;
  - ***Enlargement*** of **breasts** and ***erection*** of **nipples.**
  - ***Growth*** of **body hair**, *most prominently* **underarm** and **pubic** hair.
  - ***Greater*** **development** of **thigh muscles** *behind the* **femur**, rather than front.
  - ***Widening*** of **hips**, lower waist to hip ratio than adult males.
  - **Fat deposits**, mainly ***around*** the **buttocks**, **thighs** and **hips**.



Function

Metabolism

- **Lipid**; - ↑ **HDL**, ↑ **triglyceride** and *slight* ↓ **LDL.**
  - ↓ ***total*** **plasma cholesterol *levels*.**
- **Protein**; ↑ **hepatic *production*** of **binding proteins.**
- **Bone**; ↓ **bone resorption** and ↑ **bone formation.**
- **Skin** and **blood vessels**; ***maintenance*** *normal* **structure** and **function.**

Blood Coagulation

- ↑ **Factors II, VII, IX** and **X.**
- ↑ **Plasminogen.**
- ↓ **Antithrombin III.**
- ↓ **Platelet *aggregation*.**

Endocrine

- **Female**;
  - **Early phase of cycle** (*low* **Estrogen**) → ↓ **GnRH, FSH** and **LH.**
  - **Mid cycle** (*high* **Estrogen**) → ↑ **LH *surge*.**
  - **Luteal phase** (*low* **Estrogen**) → ↓ **GnRH, FSH** and **LH.**
  - ***Exogenous*** **estrogen** → ↓ **GnRH, FSH** and **LH** → ↓ **follicle *maturation*** → ↓ **ovulation** (**contraception**).
- **Male**;
  - ***Inhibits*** **GnRH, FSH** and **LH** → ↓ **Testosterone.**

Others

- **Fluid balance**;
  - **Sodium** and **water *retention*.**
  - ***Increase*** **Cortisol.**
- **Gastrointestinal**;
  - ***Reduce*** **bowel motility**;
    - Menstruation (menses); ↓ estrogen → ↑ bowel symptoms.
    - Pregnancy; ↑ estrogen → *Exacerbation* of constipation.
    - Oral contraceptives (estrogen); ↓ abdominal symptoms at menses.
- **Cancer**; Estrogens are implicated in various estrogen-dependent conditions, such as ER-positive breast cancer.
- **Brain**; Estrogens are implicated in sex drive, cognition, behavior and mental health.

Estrogen Preparations

Natural Estrogens

Micronized Estradiol (Estrace®)	**Estradiol** *Transdermal* (Estraderm®)
Estradiol Benzoate (Agofollin®)	**Estradiol Cypionate** (Depo-Estradiol®)
Estradiol Valerate (Delestrogen®)	**Conjugated Estrogens** (Premarin®)
Estradiol Hemihydrate (Fem 7®)	

- **Estradiol** [ess-tra-DYE-ole] **orally** is ***rapidly* metabolized** (and partially inactivated) by the ***microsomal* enzymes** of the **liver**.
- ***Micronized* Estradiol tablets** (and vaginal cream) is ***available*** and has ***better* bioavailability** and can be taken ***sublingually** instead of* **orally**.
- ***Transdermal* Estradiol** is *available* in the forms of **topical gels**, **patches**, **sprays** and **emulsions**.
- **Ester *prodrug*** of **Estradiol** such as **Estradiol Benzoate**, **Estradiol Cypionate** and **Estradiol Valerate** can be administered by **IM injection**, which a **long-lasting *depot* effect** *occurs*.
- **SC implant Estradiol** (Encore®) is alos *available*.
- **Conjugated Estrogens** (Premarin®) (**Pre**gnant **mar**e's ur**in**e); is a ***mixture*** of the **sodium salts** of **estrogen conjugates**, such as **Estrone Sulfate** and **Equilin Sulfate** *obtained from* **urine** of **pregnant mares**. It is available in **oral**, **IV**, **IM**, and **topical** *preparations*.
- **Estradiol Hemihydrate** is ***more* hydrated** (***more* insoluble** in **water**), which results in ***slower* absorption** *rates* with *specific formulations* such as **patch** (Fem 7®).

Synthetic Estrogens (Steroidal)

Ethinyl Estradiol	**Mestranol**	**Quinestrol**

Synthetic Estrogens (Non-Steroidal)

Diethylstilbestrol	**Chlorotrianisene**	**Methallenestril**

- **Ethinyl Estradiol** [ETH-ih-nil ess-tra-DYE-ole] is the ***most* effective oral Estrogens** at ***lower* doses** (less first-pass metabolism).
- **Mestranol** is a ***prodrug*** of **Ethinyl Estradiol** formulated in ***combination with*** a **Progestin** in **birth control pill** (not available alone);
  - It was the estrogen component in the first birth control pill, such as mestranol/noretynodrel (Enovid®).
  - In 1969, mestranol was replaced by Ethinylestraidol in most birth control pills.
- **Quinestrol** is a ***prodrug*** of **Ethinyl Estradiol** (ethinylestradiol 3-cyclopentyl ether).
- **Diethylstilbestrol**, **Chlorotrianisene** and **Methallenestril** are a ***synthetic* nonsteroidal estrogen**.

Enovid
SEARLE
CANADA

First approved by FDA in 1957

Therapeutic Uses

- **Hormone Replacement Therapy**;
  - Menopausal symptoms (Hot flashes, vaginal atrophy and osteoporosis).
  - Under developed female secondary sex characters (Hypogonadism).
  - Transgender women (feminizing hormone therapy).
- **Birth control**; alone or in combination with progesterone as contraceptives.
- **Prostate cancer**; by suppressing testosterone levels.
- **Breast cancer**; High-dose estrogen therapy (rarely used; tamoxifen is preferred).
- ***Others***; - Suppress lactation.
  - Girls with constitutional tall stature.
  - Estrogen replacement therapy may improve Schizophrenia and Alzheimer's symptoms in women.

Side Effects

- ***Most Common***; **Nausea**, **headache** & **breast tenderness** (**fluid retention**).
- **Uterine bleeding** (to avoid; use smallest amount of estrogen possible).
- ***Risk of*** **thromboembolic events** and **myocardial infarction**.
- ***Risk of*** **breast** and **endometrial cancer**;
  - ***Should not*** be **used** in *patients with* **estrogen-dependent neoplasms**.

Selective Estrogen Receptor Modulators (SERMs)

- **Selective estrogen receptor modulators** (**SERMs**) are a **class of drugs** that *act on* the **estrogen receptor**, *produce* **estrogenic** and **anti-estrogenic effects** ***depending on*** the **specific tissue** (**mixed estrogen agonist/antagonist; EAA**).
- **SERMs** provide the ***beneficial effects*** of **Estrogen** ***without*** the **potentially adverse** ***outcomes***.
- **SERMs** are ***used dependent*** on their **pattern of action in various tissues:**

SERMs	Generation	Uses	Estrogen Receptor; Location
Clomiphene	First	Ovulation Induction	***Antagonist***; hypothalamus.
Tamoxifen **Toremifene**	First	Breast Cancer	***Agonist***; bone and uterus. ***Antagonist***; breast.
Raloxifene	Second	Osteoporosis - Breast Cancer	**Agonist** (***full***); bone. ***Antagonist***; breast and uterus.
Ormeloxifene	Third	Contraception (Only in India)	***Agonist***; bone. ***Antagonist***; breast and uterus.
Lasofoxifene	Third	Osteoporosis - Breast Cancer - Vaginal Atrophy (Only in Lithuania and Portugal)	***Agonist***; bone ***Antagonist***; breast and uterus.
Ospemifene	Third	Vaginal Atrophy - Dyspareunia	***Agonist***; bone ***Antagonist***; breast and uterus.
Bazedoxifene	Third	Osteoporosis (Combined with conjugated estrogens)	***Agonist*** (***full***); bone. ***Antagonist***; breast and uterus.
Arzoxifene	Third	Osteoporosis (*clinical phases*)	***Agonist*** (***full***); bone. ***Antagonist***; breast and uterus.

Clomiphene (Clomid®)

- **Clomiphene** [KLOE-mifeen] is **used** to ***induce*** **ovulation** in **infertility** in **women**.
- It is *act by* ***increase*** **production** of **gonadotropins** (**FSH & LH**) by ***inhibiting*** **negative feedback** of **estrogen** on the **hypothalamus** (***block*** **estrogen receptor** in **hypothalamus**).
- ***Dose***; - **1 tab.** (**50 mg**) ***daily for*** **5** days, ***should be*** **started** ***on*** or ***about*** the **5th day** of **woman's cycle.**
  - ***If no ovulation*** → *given* **100 mg** ***daily for*** **5** days *at the next* **cycle.**
- ***Side effects***; *Reversible* **ovarian enlargement** and **vasomotor flushing** (>10%).
- ***Warning***; ***Risk of*** **ovarian enlargement & ovarian hyperstimulation syndrome.**
- ***Use*** of **Clomiphene increases** the **risk** of **multiple births** (**twins** or **triplets**).

Raloxifene (Evista®)

- **Raloxifene** is a **SERM** ***approved for*** the ***prevention*** and ***treatment*** of **osteoporosis in postmenopausal women**. It has ***estrogen-like effects*** on **bone** & ***estrogen antagonist effects*** on **breast** & **endometrium**.
- It is ***FDA-approved*** for ***reduction*** in **risk** of **invasive breast cancer**.
- **Raloxifene** causes some ***positive*** **lipid effects**.
- ***Dose***; **60 mg orally** ***once*** a **day**.
- ***Common side effects***; **hot flashes** and **leg cramps**.
- ***FDA black box warning***; ***risk*** of ***venous thromboembolism*** and **death** *due to* **stroke**.
- ***Contradictions***; **lactating women** or **pregnant women** (**Category X**) and in **women** with ***active*** or ***past history*** of **venous thromboembolic events**.

Tamoxifen (Nolvadex®) | Toremifene (Fareston®)

- **Tamoxifen** [tah-MOKS-ih-fen] and **Toremifene** [tore-EM-i-feen] have ***estrogenic effects*** in **bone** and **uterus** and ***estrogen antagonist effects*** on **breast**.
- **Tamoxifen** is ***taken orally*** *daily* for **5 years** for **breast cancer**.
- ***Off-label*** use of **Tamoxifen**; **Ovulation induction**; **5-40 mg** ***every*** **12 hrs** for **4 days**; **3rd-7th** of **cycle**.
- **Tamoxifen** is ***metabolized*** by the **CYP450** (**CYP2D6** and CYP3A4) into ***active*** **metabolites**;
- **Tamoxifen** has the ***potential*** to *cause* **Endometrial Cancer**.
- ***Common side effects***; **Hot flashes, nausea/vomiting, vaginal bleeding discharge, bone pain** and **thromboembolism.**
- **Fulvestrant** [fool-VES-trant] (**Faslodex®**)is a ***selective*** **Estrogen Receptor Degrader** (**SERD**), it **works** by ***binding*** to the **estrogen receptor** and ***destabilizing*** **it**, and ***downregulates*** **estrogen receptors** and ***inhibits*** **breast tumor** ***growth.*** It is ***given*** **IM** for **Hormone Receptor–Positive** ***advanced*** **Breast Cancer**.

Progestins

Progesterone

- **Progesterone** [proe-JESS-te-rone] is the ***most important*** **progestin** in **humans.**
- **Progesterone** ***serves*** as a ***precursor*** to the **Estrogens**, **Androgens** and **Adrenocortical Steroids**.
- It is ***synthesized*** in the **ovary** (corpus luteum), **placenta** (***large*** **amounts** *during* **pregnancy**), **testis** and **adrenal cortex** in ***response to*** **LH**.

Normal Values

- ***Reference*** **Ranges** of **Progesterone** ***Levels*** in **Adults**;
  - **Male**; 0.3 ng/mL.
- ***Premenopausal*** **Female**;

Early follicular	Late follicular	Mid-cycle	Luteal
0.6 ng/mL	14.5 ng/mL	16.1 ng/mL	31.4 ng/mL

- ***Postmenopausal*** **Female**; 0.2 ng/mL.

Pharmaco Kinetics

- ***Absorption***;
  - ***Micronized*** **Progesterone** is ***rapidly*** **absorbed** *after* **oral administration**
  - It is also available in the form of vaginal or rectal suppositories, topical creams and gels, oil solutions for IM injection.
- ***Metabolism*** and ***Excretion***
  - **Progesterone** is ***metabolized*** to **Pregnanediol** and ***conjugated*** *with* **Glucuronic Acid** and **excreted** ***into*** the **urine.**

Mechanism OF Action

- *Like* ***all*** **Steroid Hormones**, **Progestins** ***readily*** **diffuse** *across* the **cell membrane**. Once ***inside*** the **cell**, they **bind** to and ***activate*** **progesterone receptors** to *form* **receptor-hormone complex**.
- The **receptor-hormone complex** bind to a ***specific*** **sequence** of **nucleotides**, called **progesterone response element (PRE)**, which in *turn* ***modulate*** the **expression** of ***many*** **genes**.

Function

Female Reproductive System

- **Uterus**;
  - *Helps* ***implantation*** and ***formation*** of **placenta.**
  - ***Maintains*** **pregnancy** by:
    - ***Preparing*** the **endometrium** for ***implantation***.
    - ***Inhibit*** **uterine** ***contraction***.
    - ***Decrease*** **myometrium** ***sensitivity*** to **Oxytocin**.
- **Fallopian Tube**;
  - ***Stimulate*** **mucus** ***secretion*** for ***nutrition*** of the ***fertilized*** **ovum** ***during*** its **migration.**
- **Vagina**;
  - ***Stimulate*** **thick** ***secretion***, *making it thick* and ***impenetrable*** to **sperm.**

Metabolism

- **Carbohydrate**;
  - ↑ basal insulin levels and the insulin response to glucose.
  - ↑ glycogen storage by facilitating the effect of insulin.
  - ↑ ketogenesis.
- **Protein**; little effect on protein metabolism.
- **Fat**; stimulates lipoprotein lipase activity → fat deposition.

Other Effects

- ***Decrease*** **Na^+ reabsorption**; by compete with aldosterone for the mineralocorticoid receptors.
- ***Increases*** **body temperature** (unknown mechanism, but may alteration of the temperature-regulating centers in the hypothalamus).
- ***Decreases*** **plasma levels** of *many* **amino acids** and leads to ***increased*** *urinary* **nitrogen excretion.**

Progestin Preparations

Progesterone and Derivatives

Progesterone (Prontogest®)	**Medroxyprogesterone** (Provera®)
Medroxyprogesterone Acetate (Depo-Provera®)	
Hydroxyprogesterone Caproate (Proluton®)	**Megestrol Acetate** (Megace®)

- **Medroxyprogesterone** [me-DROX-ee-proe-JES-ter-one] **Acetate** ***injections*** is **used** ***once*** *every* **3 months** as **birth control** and in **endometriosis**.
- **Hydroxyprogesterone Caproate** [hye-droks-ee-proe-JES-te-rone CAP-ro-ate] is **used** ***once*** **weekly** to ***prevent*** **preterm birth** in **pregnant**.
- **Megestrol** [meh JESS troll] **Acetate** is **used** ***mainly*** as an **appetite stimulant** to treat **wasting syndromes** and *also* ***used*** in the treatment of ***advanced*** **breast cancer** and **endometrial cancer**.

First Generation Progestins

Norethisterone (Primolut® N)	**Norethisterone Acetate** (Primolut-Nor®)
Norethynodrel (Enovid®)	**Lynestrenol** (Exluton®)
Ethynodiol Diacetate (Demulen®)	

- These compounds *known as* **19-Nortestosterone** ***derivatives***.
- **Norethindrone** [nor-ETH-in-drone] or **Norethisterone** was the ***first*** **orally** *highly active* **progestin**.
- **Norethisterone** and **Lynestrenol**; ***Low*** **progestational** ***activity***, ***slight*** **estrogenic** ***activity*** & ***more*** **androgenic** ***activity***.
- **Ethynodiol Diacetate**; ***Medium*** **progestational** ***activity***, it has ***minor*** **estrogenic effects** and ***little*** **androgenic** ***activity***.

Second Generation Progestins

Norgestrel (Ovral®)	**Levonorgestrel** (Microlut®)

- **Norgestrel** [nor-JEStrel] is a ***mixture*** of both **Dextronorgestrel** (***inactive***) and **Levonorgestrel** (***active***).
- **Norgestrel** is a **19-Nortestosterone** ***derivatives***.
- **Levonorgestrel** is the ***most*** **widely prescribed** contraceptive **progestin** *worldwide*.
- It has ***high*** **progestational** and **androgenic effects**.
- It is ***Used in*** **birth control** has also been ***FDA approved*** for **emergency contraception**.

Third Generation Progestins

Desogestrel (Cerazette®)	**Norgestimate** (Cilest®)
Gestodene (Gynera®)	**Etonogestrel** (Nexplanon®)

- **Desogestrel** [des-oh-JES-trel], **Norgestimate** [nor-JES-tih-mate], **Gestodene** [JES-to-deen] and **Etonogestrel** [e-toe-noe-JES-trel] are ***high*** **progestational** ***selectivity***, ***minimizing*** or ***no*** **androgenic** ***effects*** and **estrogenic** ***activity***.
- They are ***less*** **negative** ***impact*** on **glucose** and **lipid metabolism**, **weight gain** and **acne**.

Fourth Generation Progestins

Dienogest (Visanne®)	**Drospirenone** (Yasmin®)
Segesterone Acetate (Nestorone®)	**Nomegestrol Acetate** (Lutenyl®)
Trimegestone (Totelle®)	**Norelgestromin** (Evra®)

- **Dienogest** [dye-EN-oh-jest] has ***high*** **progestational** ***selectivity*** with ***some*** **antiandrogenic** ***activity***, which may help to ***improve*** **androgen-dependent symptoms** *like* **acne**.
- **Drospirenone** [dro-SPY-re-nown] has ***high*** **progestational** ***selectivity*** with **antimineralocorticoid** ***effects***, leading to ***decreased*** **salt** and **water retention** *caused by* the **estrogen** in **birth control pills**.
- **Segesterone Acetate** *available* ***only*** as **implant**.
- **Nomegestrol Acetate** and **Norelgestromin** has ***some*** **antiandrogenic** ***activity***.
- **Trimegestone** has ***weak*** **antiandrogenic** and **antimineralocorticoid** ***activity***.

Therapeutic Uses

- **Birth control**;
    - Alone or in combination with Estrogen as contraceptives.
    - Stimulate thick secretion, making it thick and impenetrable to sperm.
- **Hormone Replacement Therapy**;
    - Progestins are commonly used as a component of menopausal hormone therapy in women to prevent endometrial hyperplasia and increased risk of endometrial cancer from unopposed estrogen therapy.
    - Also used in transgender hormone therapy.
- **Support pregnancy**;
    - Prevent recurrent pregnancy loss.
    - It is used for luteal support in in-vitro fertilization protocols.
- **Dysfunctional uterine bleeding** and **Endometriosis**.
- **Endometrial Cancer** and **Breast Cancer**;
    - Megestrol acetate and medroxyprogesterone acetate are effective.
- **Appetite Stimulation**;
    - Megestrol acetate are effective and medroxyprogesterone acetate is also used.

Side Effects

- ***Most Common***; **headache**, **depression**, **weight gain** and ***changes*** in **libido**.
- **19-nortestosterone Progestins** *such as* **Norethindrone** & **Levonorgestrel**; *possess* ***some*** **androgenic activity** (structural similarity to testosterone) and *can* **cause acne** and **hirsutism**.
- **Drospirenone** *may* **cause hyperkalemia** due to **antimineralocorticoid** *effects*.

FDA Warning

- **Estrogen** plus **Progestin** *substudy reported* an ***increased*** **risk** of **deep vein thrombosis (DVT), pulmonary embolism (PE), stroke** and **myocardial infarction (MI)** in **postmenopausal women**.
- **Estrogen** plus **Progestin** *substudy demonstrated* an ***increased*** **risk** of ***invasive*** **breast cancer**.
- The **FDA** ***recommends*** that **Medroxyprogesterone Acetate** by ***injection*** ***not*** be **used** for ***longer than*** **2 years**, due to *concerns over* **bone loss**.

Selective Progesterone Receptor Modulators (SPRM)

Mifepristone (Mifeprex®)

- **Mifepristone** [mi-FE-pris-tone] is a **Progesterone receptor** ***antagonist*** and ***partial*** **agonist activity** (in the absence of progesterone, mifepristone acts as a partial agonist) with ***powerful*** **glucocorticoid receptor** ***antagonist*** **effect**.
- ***Uses***;
    - ***Medical*** **abortion** (usually ***combined with*** **Misoprostol**); first- & second-trimester medical abortion.
    - **Emergency contraceptive**.
    - **Cushing's syndrome** (treatment of **hyperglycemia**).
- ***Most common side effects***; **Abdominal pain, cramping, nausea/vomiting, headache** and **vaginal spotting**.

Ulipristal Acetate (Ella®)

- **Ulipristal Acetate** [ue-li-PRIS-tal AS-e-tate] is a **SPRM** ***used*** for **Emergency Contraceptive** (within 120 hours; 5 days of sex) and **Uterine Fibroids**.

Vilaprisan	Asoprisnil	Telapristone

- **Vilaprisan**, **Asoprisnil** and **Telapristone** are **SPRM** ***under*** **development**.

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Gynecology

(GYNECOLOGY)

Subject	No. of page
Contraceptive Methods	963
Dysmenorrhea	972
Premenstrual Syndrome (PMS)	974
Endometriosis	976
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Menopause	983
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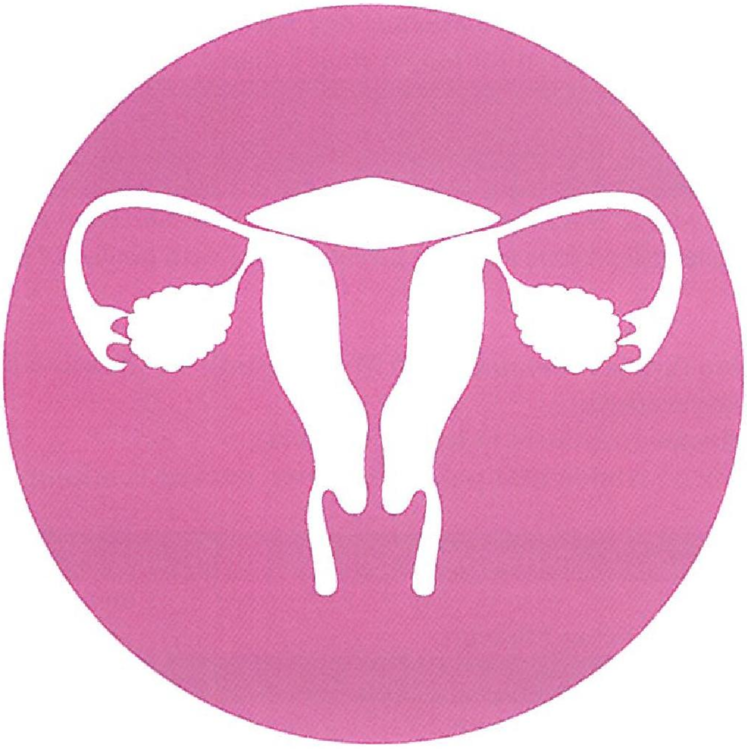
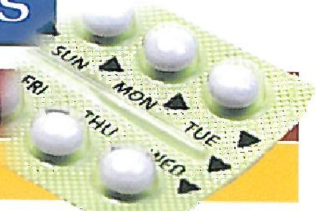


Contraceptive Methods

I- Hormonal Contraceptives.
II- Vaginal Spermicides.
III- Barrier Contraceptives.
IV- Intrauterine Devices.
V- Sterilization Methods.
VI- Natural Methods.
VII- Emergency Contraceptives.

Which Contraceptive is good for US?
FIND OUT

I- Hormonal Contraceptives



1- Oral Contraceptives (Oral Pills)

A) Combined Oral Contraceptive Pill (COCP)

Monophasic Combination

- ***Containing*** a ***fixed*** ration of **Estrogen** and **Progestin** given ***daily*** for **21 days**, ***beginning on*** **day 5** of the **menstrual cycle**.

Example

1) ↑ dose of E & P; Primovlar®

Ethinyl Estradiol	0.05 mg
Norgestrel	0.5 mg

2) ↓ dose of E and P

Microvlar® - Microcept®

Ethinyl Estradiol	0.03 mg
Levonorgestrel	0.15 mg

Gynera®

Ethinyl Estradiol	0.03 mg
Gestodene	0.075 mg

Cilest®

Ethinyl Estradiol	0.035 mg
Norgestimate	0.25 mg

Yasmin®

Ethinyl Estradiol	0.02 mg
Drospirenone	3 mg

3) ↓ dose of E and ↑ dose of P

Loestrin®

Ethinyl Estradiol	0.03 mg
Norethisterone	1.5 mg

Biphasic Combination

- ***Containing*** a ***fixed dose*** of **Estrogen** (**days 1-21**).
- OR ***Containing*** a ***different dose*** of **Progestin** (**days 1-10**) ***lower than*** (**days 11 -21**).

Example

Necon®

Light yellow tablet (10 tablets)

Norethindrone	0.5 mg
Ethinyl Estradiol	0.035 mg

Dark yellow tablet (11 tablets)

Norethindrone	1 mg
Ethinyl Estradiol	0.035 mg

Triphasic Combination

- ***Containing*** ***3 different*** **doses** *gradual* **Estrogen** ***increase*** and/or ***some*** **pills** may also ***increase*** the **dose** of **Progestin**.

Example

Triocept®

6 Tablets

Levonorgestrel	0.05 mg
Ethinyl Estradiol	0.03 mg

5 Tablets

Levonorgestrel	0.075 mg
Ethinyl Estradiol	0.04 mg

10 Tablets

Levonorgestrel	0.125 mg
Ethinyl Estradiol	0.03 mg

- The ***last*** **7 days** of the **cycle** are **hormone** ***free*** **days**.
- ***Other*** **packets** *contain* **7** ***additional*** **placebo pills** (***inactive*** **pills**).
- ***Some*** **newer formulations** have **24 days** of ***active*** **hormone pills**, *followed by* **4 days** of **placebo** (*example*; **Yaz® 28**; Ethinyl estradiol 0.02 mg and Drospirenone 3 mg).

Four-phasic Oral Contraceptive

Natazia®; Estradiol Valerate and Dienogest
Quartette®; Ethinyl Estradiol and Levonorgestrel

- Provide 4 different doses of progestin/estrogen during a 28-day cycle.

Extended (or Continuous) Cycle Combined Hormonal Contraceptive

Seasonale®; 0.03 mg Ethinyl Estradiol and 0.15 mg Levonorgestrel

- Contains 84 days of active pills and 7 days of inactive (placebo) pills.

Seasonique®; 0.03 mg Ethinyl Estradiol, 0.01 mg Ethinyl Estradiol and 0.15 mg Levonorgestrel

- Contains 84 days of active pills and 7 days of low-dose estrogen pills.

Lybrel®; 20 mcg Ethinyl Estradiol and 90 mcg Levonorgestrel

- Contains a full year of active pills with no inactive pills.

B) The Mini-Pill (Progestin Only Pill; POP)

Microlut® (0.03 mg Levonorgestrel) - **Micronor®** (0.35 mg Norethindrone)
Exluton® (0.5 mg Lynestrenol) - **Cerazette®** (75 mcg Desogestrel)

- **Progestin** ***only*** is *given for* **28 days** ***continuously***. These **pills** ***contain*** a ***smaller*** *amount* of **Progestin.**
- It is ***less effective*** than **COCP**, *especially* if ***one*** or ***more*** **tablets** are ***missed***.
- ***Good choice*** in **patient** who are ***unable*** to take **estrogen** (due to **estrogen** ***related*** **side effects**).

C) Sequential Method

- *Start by* **estrogen** ***alone*** for 14-16 days, then ***combination*** of **estrogen** and **progestin** for 5-6 days.

D) Post-Coital (Morning After Pills)

- *See* **Emergency Contraceptive** (*next*).

Mechanism OF Action

- The ***dominant*** **mechanism** of ***combinations*** of **Estrogens** and **Progestins**;
  - ***Prevent*** **ovulation** by ***suppressing*** the **gonadotropin-releasing hormone (GnRH)** from the **hypothalamus** and **gonadotropins (FSH** and **LH)** from the **anterior pituitary** *via* **negative feedback.**
- *All* **Progestogen**-***containing*** **contraceptives** *produce*;
  - ***Prevent*** **ovulation** *via* **negative feedback.**
  - ***Increase*** **thick** ***secretion*** of **cervical mucus** → ***Resist*** **sperm motility**.
  - **Endometrial changes** and ***inhibition*** of **fallopian tube** ***motility*** → ***Resist*** **sperm motility** and ***inhibit*** **implantation.**

Therapeutic Uses

- **Birth control.**
- **Polycystic Ovary Syndrome** (**PCOS**); to control menstrual irregularity.
- **Dysmenorrhea**; to treat cramping and pain associated with primary dysmenorrhea.
- **Endometriosis**; to treat pelvic pain and suppress the growth of the extra-uterine endometrial tissue.
- **Acne** and **Hirsutism**; decrease androgen production by the ovaries and rise production of sex hormone binding globulin that binds to androgens and reduces their activity.

Pharmacological Action

- **Ovary**;
  - ***Chronic use*** of **COCPs** → **depresses ovarian function.**
  - **Ovaries** *become* ***smaller*** (even if enlarged before therapy).
  - **Patients** ***return*** to ***normal*** **menstrual patterns** when these **drugs** are ***discontinued*** (About 2% of patients remain amenorrheic for up to several years after discontinued).
- **Uterus**;
  - **Uterine bleeding** (**spotting** or **breakthrough bleeding**), ***especially*** with ***low dose*** **preparations**;
    - *If* spotting occurs ***before*** **mid-cycle** → ↑ **Estrogens dose.**
    - *If* spotting occurs ***after*** **mid-cycle** → ↑ **Progestins dose.**

    * **Biphasic** and **Triphasic preparations** ***decrease*** **breakthrough bleeding** ***without*** **increasing** the ***total*** **hormone content.**
  - ***Chronic use*** of **COCPs** → **cervix hypertrophy** (*risk of* **cervical cancer**).
- **Breast**; In small doses the effects on breast are not appreciable.
  - **Estrogen** ***stimulate*** **breast enlargement.**
  - **COCPs** → ***suppress*** **lactation.**
- **CVS**;
  - **Hypertension**;
    - **Na$^+$** and **water retention** (*due to* ↑ **activity renin angiotensin system**).
    - *Small* ***increases*** in **cardiac output.**
  - *Risk of* **Myocardial Infarction** (↓ **HDL**);
    - **Estrogen** → ↑ **HDL** and ↑ **triglyceride.**
    - **Progestin** → ↓ **HDL** and ↓ **triglyceride.**
    - **COCPs** → ***slightly*** ↓ **triglycerides** and **HDL.**
  - *Risk of* **Venous Thromboembolic Disease**:
    - **Estrogen** → ↑ **VII, VIII, IX** and **X factors** and ↓ **antithrombin III.**

Pharmacological Action

- **CNS**;
  - **Depression**, **irritability** and **loss** of **libido** (*mainly due to* **progestin**);
    - ☞ ↑ Requirement of vitamin B6 is important to relive depression symptoms.
  - **Vascular headache** (**migraine**).
- **GIT**;
  - **Nausea** and **vomiting**;
    - ***Management*** of **pill-*associated*** **nausea** *include*:
      - ☞ **Use *low dose*** of **estrogen** *containing* **oral contraceptive**.
      - ☞ ***Taking*** the **pill** at **bedtime**.
  - ***Reduce* bowel motility**; ↓ **abdominal pain** *associated with* **dysmenorrhea**.
- **Skin**;
  - **Breast tenderness** (*due to* Na^+ & **water *retention***).
  - ***Increase* pigmentation** (**Chloasma**).
  - **Acne** and **Hirsutism** (*due to* **androgenic activity** of ***some*** **progestins**).
  - **Weight gain** (*due to* **anabolic effect** of **androgenic activity** of **progestins**).
- **Endocrine**;
  - ***Inhibition*** of **pituitary gonadotropins**.
  - ***Increase*** **activity** of **renin-angiotensin aldosterone system**.
  - ***Increase*** **cortisol-binding globulin** (**CBG**) [high doses of estrogen] → ↑ total plasma concentrations and ↑ urinary excretion of free cortisol.
  - ***Increase*** **thyroxine-binding globulin** (**TBG**) → ↑ total plasma T4 levels, but free thyroxine level is normal.
  - ***Increase*** **sex hormone-binding globulin** (**SHBG**) → ↓ free androgens.
- **Carbohydrate Metabolism** (**Progestins**);
  - ↓ rate of carbohydrate absorption from GIT.
  - ↑ basal insulin levels and the insulin response to glucose.
- **Liver**;
  - **Cholelithiasis** (**Gallstones**) and **Cholestasis** (**Cholestatic jaundice**); due to ***changes*** in **bile composition** (↑ cholic acid & ↓ chenodeoxycholic acid in bile).
  - **Hepatic adenomas** are *associated with* **long-term use**.

Side Effects

A) ***Mild*** **Side Effects**;

- **Nausea**, **breakthrough bleeding** and **breast tenderness**; are related to the amount of estrogen in the preparation.
- **Headache**; is mild and often transient.
- ***Changes*** in **serum proteins** and other effects on endocrine function.

B) ***Moderate*** **Side Effects**; *may* ***require*** **discontinued**;

- **Breakthrough bleeding** (about 25% of patients); **Biphasic** and **Triphasic preparations** ***decrease*** **breakthrough bleeding** ***without*** **increasing** the ***total*** **hormone content**.
- **Weight gain**; is *more common* with **androgen-like progestins**.
- **Acne** and **Hirsutism**; is *more common* with **androgen-like progestins**.
- ***Increased* skin pigmentation**; especially in dark skinned women.
- **Ureteral dilation** (**bacteriuria**) and **vaginal infections**.
- **Amenorrhea**; Following withdrawal of oral contraceptives;
  - 95% of patients with normal menstrual histories resume normal periods.
  - Some patients resume normal cycles during the next few months.
  - Few patients remain amenorrheic for several years.

C) ***Severe*** **Side Effects**;

- **Venous thromboembolic disease**.
- **Myocardial infarction**.
- ***Increased*** **risk** *of various* **cardiovascular disorders**.
- **Cholestatic jaundice** and **gallstones**.
- **Depression**.
- ***Risk*** *of* **hepatic adenomas**.
- ***Risk*** *of* **cervical cancer** and **breast cancer**.

Contra indication

- **Estrogen dependent neoplasms.**
- ***History of* thromboembolic diseases.**
- ***History of* myocardial infarction.**
- ***Impaired* liver function** or *post history* of **cholestatic jaundice.**
- ***Undiagnosed abnormal* genital bleeding** and **Pregnancy.**
- **Diabetes mellitus, Hypertension, Migraine, Depression** and **Obesity.**

Drug Interactions

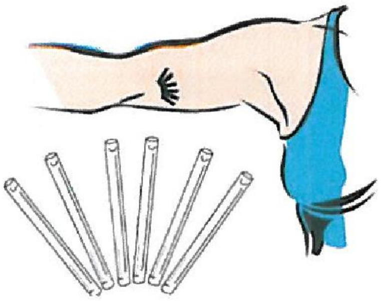
- **Important Interactions;**
  - **Drugs ↑ COCP concentrations:**
    - **Ascorbic acid** (**Vitamin C**) and **Paracetamol** (**Acetaminophen**).
  - **Drugs ↓ COCP concentrations:**
    - **Broad spectrum antibiotics** (↓gastrointestinal flora → ↓ COC absorption due to ↓ enterohepatic cycling).
    - **Liver microsomal enzyme *inducers*** e.g. **Barbiturates, Rifampicin Phenytoin, Valproic acid** and ***several* anticonvulsant drugs.**

2- Injection Contraceptives

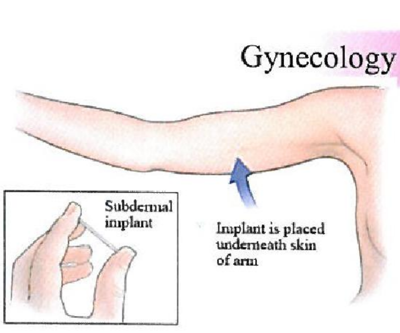
- The **injection contraceptives** *mainly contains* **Progestin.**
- **Efficacy**; *over* **99%** effective (**Depo-Provera®** is **99.7%** *effective*).
- **One** *injection* can *protect for* **1, 2** or **3 months** *depending on* the *type of* **preparation.**
- **Depo-Provera®** is the ***most commonly*** **used contraceptive injection.**
- **Preparations**;
  - **Depo-Provera®150 mg Depot Medroxyprogesterone Acetate (DMPA) → IM** *every* **3 months.**
  - **Sayana Press® 104 mg Depot Medroxyprogesterone Acetate (DMPA) → SC** *every* **3 months.**
  - **Noristerat®; 200 mg Norethisterone Enanthate; → IM** *every* **2 months.**
  - **Mesigyna®; 50 mg Norethisterone Acetate + 5 mg Estradiol Valerate → IM** *every* **1 months.**
- **Advantages**; **Depo-Provera®**
  - ***Useful*** in **patients** *with* (safe in women with a contraindication to estrogen);
    - **Hepatic disease, hypertension** or *prior* **thromboembolism.**
    - **Diabetes mellitus** *with* **complications** and **migraine headaches.**
    - **Epilepsy** *treated with* **medications** that ***induce*** **hepatic enzymes.**
  - **Dysmenorrhea symptoms** is ***decreased.***
  - ***Risks*** of **endometrial** and **ovarian cancer** are ***decreased.***
  - ***Safe*** for **breastfeeding mothers;**
    - **Combined oral contraceptives *should not*** be *initiated* ***before*** **six weeks *postpartum.***
- **Disadvantages**;
  - **Menstrual cycle *disruption*** and **amenorrhea** *occurs in* **50%** of **women *within*** the **first year** and it can ***delay*** the **return** to **fertility.**
  - ***Reduction*** in **bone density** (**black box warning**); due to ***suppression*** of *endogenous* **estrogen *secretion.***
  - **Weight gain.**

3- Contraceptive Implants

- **Contraceptive implants** are **Progestin *filled* rods** or **capsules** that are ***inserted*** *under* the **skin.**
- **Efficacy**; **99.95%** ***effective*** for ***at least*** **3 years.**
- **Preparations** (size of a matchstick);
  - **A) First Generation (6 Rods system); Norplant® I;**
    - Consisted of a set of 6 small (2.4 mm × 34 mm) silicone capsules.
    - Each filled with 36 mg of **Levonorgestrel**.
    - Implanted sub-dermally in the upper arm.
    - Effective for 5 years.
    - It was removed from the market in 2002 due to side effects.



  - **B) Second Generation (2 Rods system); Jadelle® - Norplant® II**
    - Consists of 2 small (2.5 mm × 43 mm) silicone rods.
    - Each containing 75 mg of **Levonorgestrel** in a polymer matrix; Implanted sub-dermally in the upper arm.
    - Effective for 5 years.


Subdermal implant
Implant is placed underneath skin of arm

C) Second Generation (1 Rod system);

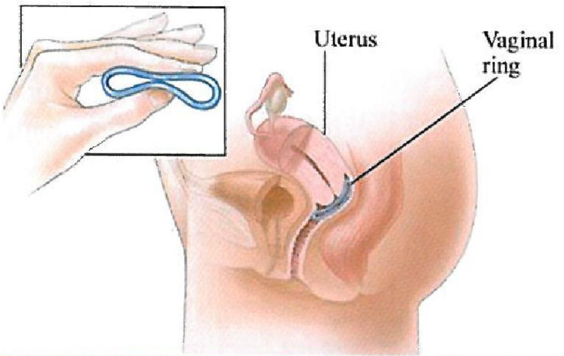
Implanon® and Nexplanon®

- It is a newer form of the contraceptive implant.
- It is contains 68 mg of **Etonogestrel** (Progestin; Desogestrel is a prodrug of Etonogestrel).
- Implanted sub-dermally in the upper arm.
- Effective for 3 years.

- **Advantages**; **Implanon®** and **Nexplanon®**
  - ***Safe*, 99.95% *effective*** and **easy** *to be* **use.**
  - ***Longevity*** of **effectiveness.**
  - ***Absent*** of ***exogenous*** **estrogen.**
  - ***Can be*** **removed *anytime*** *within* the **3-year period.**
  - ***After*** **removal**, a **woman's *ability*** to *become* **pregnant *returns* quickly**.
  - ***Can be*** **used** by **breastfeeding women.**
- **Disadvantages**;
  - A ***minor*** **surgical procedure** is ***necessary*** for **removal.**
  - **Menstrual irregularities** are ***common***; may be improved with NSAIDS or a short-term course of low-dose combined oral contraceptives or estrogen.
  - **Headache, breast tenderness** and **mood changes** are ***less common.***

4- Contraceptive Vaginal Rings

NuvaRing® (Etonogestrel/Ethinylestraidol)

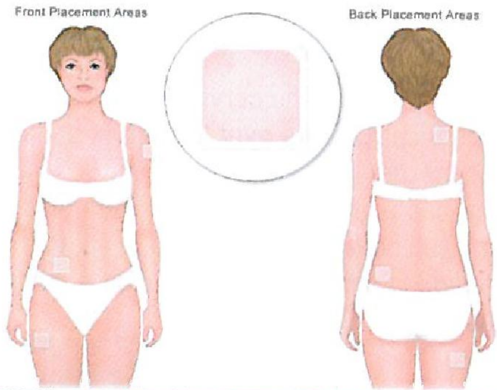

Uterus
Vaginal ring

- **Contraceptive vaginal rings** can ***deliver*** **progesterone** or **progesterone-estrogen *combinations*.**
- The **ring** is used in the same ***schedule*** as **oral contraceptives, *with* 3 weeks** of **ring usage** and **1 week *without*** to **produce** a ***withdrawal*** **bleed.**
- It is ***easily*** **inserted** and **removed** by the **woman herself**, and ***rapid*** **return** of **fertility** *upon* ***discontinuation*.**
- ***Not*** **cause nausea** and **vomiting** (due to ***no*** **first-pass effect**).
- ***Side effects***; **headaches** and **vaginal irritation** or **discharge**.

5- Contraceptive Patches

Ortho Evra® - Xulane®

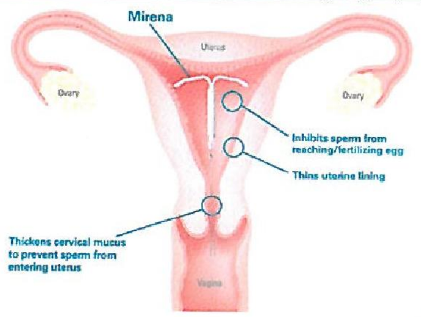
(Norelgestromin/Ethinylestraidol)


Front Placement Areas
Back Placement Areas

- The **contraceptive patch** is a **sticky patch**, *measuring* **5x5cm, *releases*** **estrogen** and **progesterone *directly*** into the **skin.**
- Each **patch *contains*** a **1-week** *supply of* **hormones.**
- ***Apply for*** **three weeks** [days 1, 8, and 15], and *then* **stop *using*** the **patch** for **seven days** [days 22-28] (**patch-free week; *withdrawal*** **bleed**).
- ***Not*** **cause nausea** and **vomiting.**

6- Hormonal Intrauterine Devices

Mirena® - Skyla®


Mirena
Uterus
Ovary
Ovary
Inhibits sperm from reaching/fertilizing egg
Thins uterine lining
Thickens cervical mucus to prevent sperm from entering uterus
Vagina

- **Hormonal intrauterine device** (IUD) is a ***small*** 'T'-shaped **device, *containing*** **Levonorgestrel**, which is ***inserted into*** the **uterus**, is ***over*** **99% effective.**
- It is the ***most effective*** types of ***long-acting reversible*** **birth control** (***no delay*** in a ***return to*** **fertility**).
- ***Very slow*** **daily *low dose*** of the **hormone.**
- ***Effective Up*** to **5 years.**

II- Vaginal Spermicides

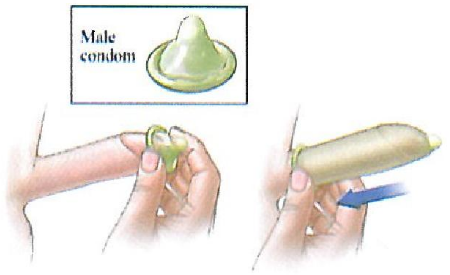
Contraseed® - NeoSampoon®

- **Spermicide** is a **contraceptive substance** that ***destroys*** **sperm**.
- The ***most common*** **active ingredient** of **spermicides** is **nonoxynol-9**.
- Are ***available*** in many **forms**, such as **gel** (jelly), **films**, **foams** and **Supps**.
- **Spermicides** are ***combined with*** **contraceptive barrier** ***methods***.

III- Barrier Contraceptives

1- Male Condom

Durex® male condom

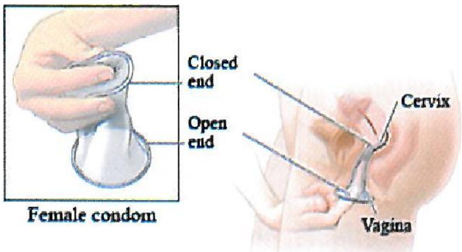


- A **condom** is a **barrier device** ***commonly used*** during **sexual intercourse** to ***reduce*** the ***probability*** of **pregnancy** and **spreading sexually transmitted diseases** (such as gonorrhea, syphilis, and HIV).
- It is put on a **man's erect penis** and ***blocks*** **ejaculated semen** from ***entering*** the **body** of a **sexual partner**.
- **Condoms** *possibly* ***decrease*** **enjoyment** of **sex**.
- **Oil-based lubricants** may ***damage*** the **condom**.

2- Female Condom

Pasante® - Ormelle®

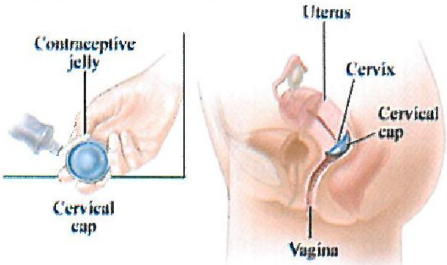
- A **female condom (femidom)** is a device that is used ***during*** **sexual intercourse**.
- Act as a **barrier contraceptive** to ***reduce*** the **risk** of **sexually transmitted diseases** and ***reduce*** the **probability** of **pregnancy**.
- It is a thin, soft, loose-fitting sheath with a flexible ring at each end.
- May cause a **urinary tract infection** if ***left*** in **vagina** for a **prolonged period**.



3- Cervical Cap

FemCap®

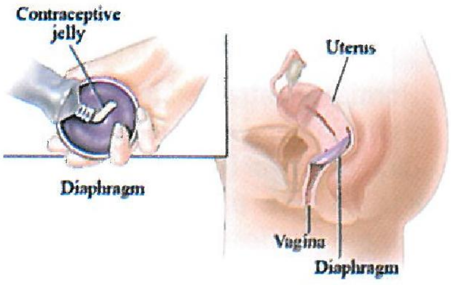
- The **cervical cap** is a *form of* **barrier contraception**.
- A **cervical cap** ***fits over*** the **cervix** and ***blocks*** **sperm** from ***entering*** the **uterus**.
- The **cap** is inserted ***at least*** **15 minutes** ***before*** **sexual intercourse** and can be ***left*** in place for ***up to*** **48 hours**.
- For ***added*** **protection**, **spermicide** is ***put*** **into** the **cap** *before* **inserting** the cap.



4- Diaphragm

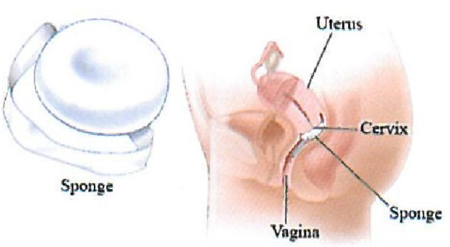
Caya® - Ortho-Diaphragm® - Koromex®

- It is a **round, dome-shaped** ***device*** made of **rubber** or **silicone** with a **firm, flexible rim**.
- It **fits** ***inside*** the **vagina** and ***covers*** the **cervix**, the ***opening*** of the **uterus**.
- It should always be used with a **sperm-killing** (**spermicide**).
- The **diaphragm** must be ***inserted*** sometime ***before*** **sexual intercourse**, and ***remain*** in the **vagina** for **6** to **8 hours** ***after*** a **man's** ***last*** **ejaculation**.



5- Contraceptive Sponge

Pharmatex® - Protectaid® - Today®



- The **contraceptive sponge** ***combines*** **barrier** and **spermicidal** ***methods*** to ***prevent*** **conception.**
- A **contraceptive sponge** ***contains*** a **spermicide** that is ***released*** *over* the **24 hours** that the **sponge** may be ***left*** in the **vagina.**
- It also ***blocks*** the **cervix** so ***sperm can't*** **pass.**

IV- Intrauterine Devices (IUDs)

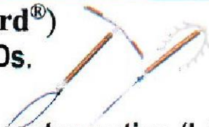
1- Hormonal IUD

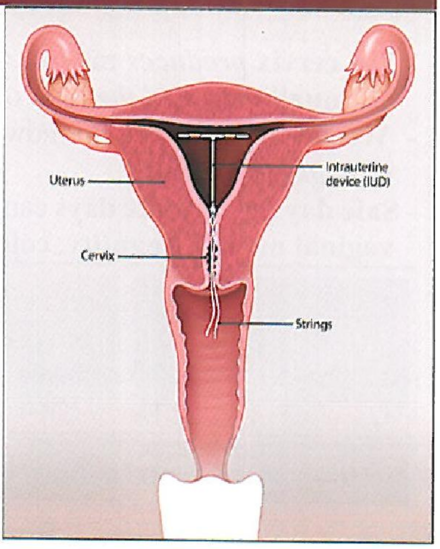
Mirena® - Skyla®

- **Hormonal intrauterine device** (**IUD**) is a ***small*** 'T'-**shaped device**, ***containing*** **Levonorgestrel**, which is ***inserted into*** the **uterus**, is ***over*** **99% effective.** ***Effective Up*** to **5 years.**

2- Copper IUD

Copper T380 (ParaGard®)





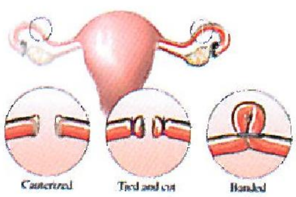
- Many ***different types*** of **copper IUDs.**
- Cu-IUDs are available in **T-shaped** and **U-shaped.**
- **Copper IUDs** are a ***form*** of **long-acting** ***reversible*** **contraception** (**LARC**) and ***effective*** forms of **birth control** (failure rate is 0.6%).
- **Copper** is ***toxic to*** **sperm.**
- It **makes** the **uterus** and **fallopian tubes** *produce* **fluid** that **kills sperm.** This ***fluid contains*** **white blood cells**, **copper ions**, **enzymes**, and **prostaglandins.**
- The **ParaGard®** can be used as a form of **emergency contraception** if **inserted** ***within*** **3-5 days** after ***unprotected*** **intercourse.**
- **ParaGard®** is ***effective*** *up to* **10 years.**
- ***Other*** **products** are ***effective*** *from* **3-5 years.**
- ***Disadvantages***;
  - ***Partial*** or ***complete*** device **expulsion.**
  - ***Risk*** of uterine **perforation** at the time of insertion (1%).
  - ***Increased*** **dysmenorrhea** (**abdominal pain** and **cramps**) and **blood loss** (occur in the first few cycles).
  - ***Risk*** of an **ectopic pregnancy.**
  - Some ***risk*** of **pelvic inflammatory disease** (**PID**); **pelvic infection.**

V- Sterilization Methods

Female Sterilization

Tubal ligation or Tubectomy

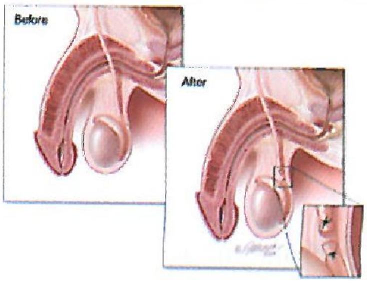
- Woman's fallopian tubes are clamped and blocked, which prevents eggs from reaching the uterus for fertilization.
- It is a permanent method of birth control.



Male Sterilization

Vasectomy

- It is a permanent birth control.
- Vasectomy is a small operation to cut the vas deferens.
- This is the tube that takes sperm from the testes to the penis.



VI- Natural Methods

- **Natural methods** of **contraception** are *considered* "**natural**" *because* they are ***not* mechanical** and ***not*** a *result of* **hormone manipulation.**

1- Abstinence

- **Abstinence** is *defined as* ***not* having *any* type** of **intercourse** or **sexual activity** with a **partner**.

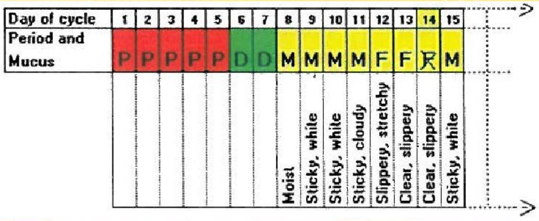
2- Fertility Awareness Methods (FAMs)

Calendar Rhythm Method

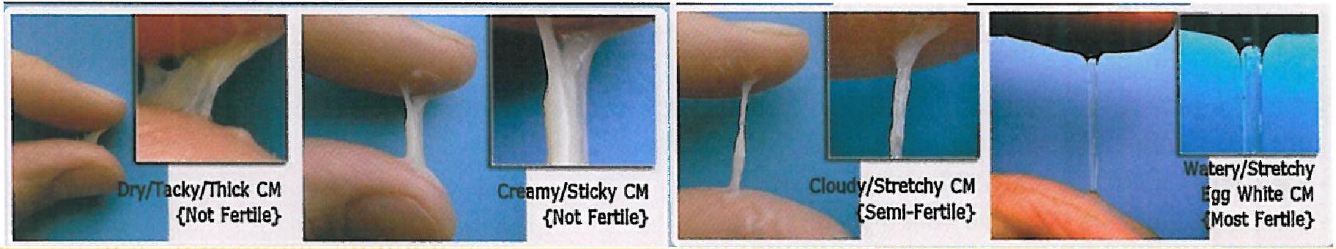
- ***Avoid* intercourse** (or *uses* **condoms**) *during* **ovulation day** (**Day 14 +/- 5 days**).
- To *determine* this *apply* the **following formula**;
  - **Woman *records* the number of days in *each* menstrual cycle for *at least* 6 months**;
    1) Woman subtracts 18 from the length of her shortest recorded cycle.
    2) Woman subtracts 11 days from the length of her longest recorded cycle.
       * If the shortest of her last 6 cycles was 27 days; 27–18 = 9.
       * If the longest of her last 6 cycles was 31 days, 31 – 11 = 20.
  - Thus, she must avoid unprotected sex from day 9 through day 20 of her cycle.

Cervical Mucus Method

- The **cervix *produces* mucus**, and it ***changes*** in **quantity** and **quality** *around the* **time** of **ovulation.**
- **Women** can be ***taught*** how to ***detect*** these **changes** *through* **instruction.**
- **Safe days** and **unsafe days** can be *determined by **tracking*** **vaginal mucus**; **quantity**, **color**, and **texture.**

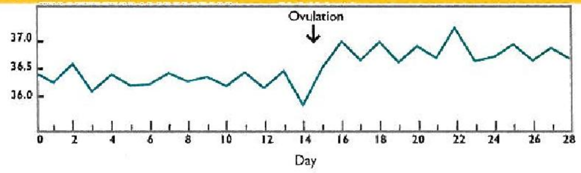


Day of cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Period and Mucus	P	P	P	P	P	D	D	M	M	M	M	F	F	F	M
								Moist	Sticky, white	Sticky, white	Sticky, cloudy	Slippery, stretchy	Clear, slippery	Clear, slippery	Sticky, white



Basal Body Temperature (BBT) Method

- **Woman's temperature *drops* 12** to **24 hours *before*** an **egg** is ***released from*** her **ovary** and then ***increases*** **again *once*** the **egg** has been ***released.***
- The couple uses condoms after woman's temperature drops and rises above regular temperature.



Symptothermal Method

- This is a ***combination*** of the **cervical mucus method**, **calendar method** and **temperature method.**

3- Withdrawal (Coitus Interruptus) Method

- **Withdrawal** is the ***behavioral action*** where a **man *pulls*** his **penis *out*** of the **vagina *before*** **ejaculates.**

4- Outercourse

- **Outercourse** is other **sexual activities *without*** **penetration intercourse.**

5- Lactational Amenorrhea Method

- **Continuous Breastfeeding (Lactational Amenorrhea Method)** is considered a form of contraception because it can ***postpone*** **ovulation** for ***up to*** **6 months *after*** **birth.**
- **Prolactin** ***prevents*** the ***release*** of the **hormone** that ***triggers*** **ovulation.**
- It is ***only*** **effective** if the **baby** is ***fully*** or ***nearly fully*** breastfed and is **fed** often, **day** and **night.**

VII- Emergency Contraceptives (ECs)

- **Emergency Contraceptive**; is a **drug** or **device** to ***prevent*** **pregnancy** ***after unprotected*** **sexual intercourse**.
- **Emergency contraceptive pills (ECPs)** *also called* **morning-after pills** or **postcoital contraceptives**.

1- Progestin-only Method

Levonorgestrel (Contraplan II® - 0.75 mg)

- **Progestin-only method** also *known as* **higher regimen method**.
- The **pills** *containing* ***high dose*** of **Levonorgestrel 1.5 mg** (2 tablets 0.75 mg).
- This **pill** typically **works *up to* 72 hours *after* intercourse**.
- **Efficacy**; **75-85%** ***effective***.

2- Yuzpe Regimen

Estrogen + Progesterone

- **Yuzpe regimen** is a ***method*** of **emergency contraception** that uses a ***combination*** of **Ethinylestraidol** and **levonorgestrel** (100 µg of Ethinylestraidol and 0.5 mg of levonorgestrel that is taken twice, with 12 hours between doses).
- It is ***less effective*** **method** and ***less commonly*** **used**.
- This **pill** works ***within*** **72 hours *after*** **intercourse**.
- **Efficacy**; *about* **75%** ***effective***.

3- Ulipristal Acetate

Ulipristal Acetate (Ella®)

- **Ulipristal** is a ***selective*** **progesterone receptor modulator (SPRM)**; has partial agonistic as well as antagonistic effects on the progesterone receptor.
- **Ulipristal Acetate 30 mg** tablet is **used *within* 120 hours (5 days) *after*** an **unprotected intercourse** or **contraceptive** *failure*.
- If **vomiting** *occurs* ***within*** **3 hours *after*** the **dose**, consider ***repeating*** the **regimen**.
- **Ulipristal Acetate 5 mg *daily*** for **13 weeks *effectively*** **controlled *excessive*** **bleeding** due to **uterine fibroids** and ***reduced*** the **size** of the **fibroids**.
- **Efficacy**; *about* **85%** ***effective***.

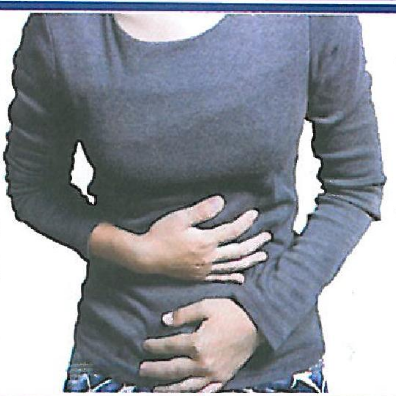
4- Mifepristone

- **Mifepristone** is an ***antiprogestogen*** (or selective progesterone receptor modulator; SPRM).
- A ***single dose*** of **10 mg** or **50 mg** (600 mg may be used) **Mifepristone effective *up to* 120 hours (5 days) *after*** **intercourse**.
- **Efficacy**; ***up to*** **85%** ***effective***.

5- Copper T380 Intrauterine Device

- **Copper T380 IUD** can be **inserted *up to* 120 hours (5 days) *after*** an **unprotected intercourse** or **contraceptive** *failure*.
- **Efficacy**; ***most effective*** **method** (failure rate of only 0.09%).

Dysmenorrhea



- **Dysmenorrhea** (**painful periods**); is **painful cramping** in the ***lower*** **abdomen** *just* ***before*** or ***during*** the **menses**.
- **Dysmenorrhea** is the ***most*** **commonly** ***reported*** **menstrual disorder**.
- ***More than*** **one half** of **women** who **menstruate** have ***some*** **pain** for **1-2 days** ***each*** **month**.
- It can be ***divided into*** **2 broad categories**: **primary** (*absence of* **pelvic pathology**) and **secondary** (*resulting from* **pelvic pathology**).

- ***Types***;

	Primary Dysmenorrhea	Secondary Dysmenorrhea
Definition	- **Menstrual pain** ***without*** **pelvic pathology**.	- **Menstrual pain** ***with underlying*** **pelvic pathology** (such as endometriosis, pelvic inflammatory disease and fibroids).
Incidence	- The ***most common*** type. - ***Begins*** **soon** *after* a **girl** ***starts*** *having* **menstrual cycle** (teens and early twenties). - **Menstruation** ***becomes*** **less painful** as *they* ***get*** **older**.	- This is ***less*** **common**. - ***More likely*** to occur in **women** in their **30s** and **40s** (***beginning after*** **25 years** of **age**).
Causes	- ***Increase*** **concentration** of ***endometrial*** **prostaglandins (PGs)** *during* **menstruation**, *due to* the ***destruction*** of the **endometrial cells**. - **Uterus contraction**. - **GI problem**.	- **Prostaglandins** ***release***. - ***Sign*** *of* ***more*** **serious disorder** in the **reproductive system** such as : - **Endometriosis**. - **Pelvic inflammatory disease**. - **Fibroids**.
Symptoms	- *Usually lasts* **12-24 hours**, *but lasts* **2-3 days** in ***some*** cases. - ***Lower*** **abdominal pain (cramping)** ***radiating*** **down** into the **thighs** and **backache**. - **GIT symptoms** (nausea, vomiting and diarrhea). - **Headache** and **Faintness**.	- The **pain** may ***actually*** **start** ***before*** **menstruation begins**; ***continue*** for the ***duration*** of **menses**. - The **pain** ***associated with***: - **Abdominal bloating** and **Backache**. - **Feeling** of **heaviness** in **pelvic area**. - ***Other*** **Gynecology symptoms**: - **Dyspareunia & Menorrhagia**.

- ***Diagnosis***;
  - **Primary Dysmenorrhea**; **medical history** of **symptoms** and **pelvic examination** is ***normal***.
  - **Secondary Dysmenorrhea**; **pelvic examination**, **laparoscopy**, **hysteroscopy**, **ultrasound examination** and **MRI**.
- ***Management***;

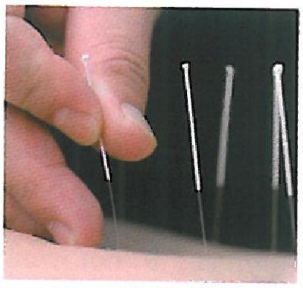
Management of Primary Dysmenorrhea

Non-Pharmacological Management

A) **Heat Therapy**;
- ***Taking*** **warm bath**.
- ***Put*** **hot water bottle** in ***lower*** **abdomen**.

B) **Dietary**, **Vitamins** and **Herbal Supplements**;
- **Vitamin B_1** is ***important for*** **metabolism**, and ***deficiency*** *can cause* **fatigue**, **muscle cramps**, **pain**, and ***reduced*** **pain tolerance** (all common symptoms of dysmenorrhea).

- **Vitamin E** is ***fat-soluble*** and has *many* **antioxidant effects**; it has been shown to ***inhibit* protein kinase C**, which is *responsible for* ***releasing*** **arachidonic acid** *from* **cell membranes, arachidonic acid** is a *precursor of* **prostaglandin synthesis**.
- **Vitamin B_6, Magnesium** and **Omega-3 fatty acids** have also been suggested to have ***beneficial*** **effects** in **women** *with* **primary dysmenorrhea**.
- **Ginger** is ***effective*** on **pain relief** in **primary dysmenorrhea**.



C) Exercise;

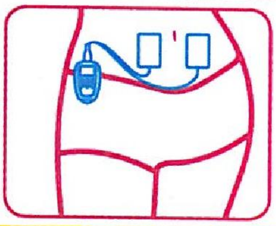
- **Exercise** has been ***shown*** to ***relief*** **symptoms** of **dysmenorrhea**, though the mechanism is not well understood.

D) Acupuncture;

- **Acupuncture** is ***effective*** for ***treating*** **symptoms** of **primary dysmenorrhea**.

E) Transcutaneous Electrical Nerve Stimulation (TENS);

- **TENS** is the use of **electric current** *produced by* a **device** to ***stimulate*** the **nerves** *for* **therapeutic purposes**.
- **TENS** was *found to* be ***effective*** for the ***treatment*** of **dysmenorrhoea** by a *number of* ***small*** **trials**.



Pharmacological Management

A) Non-steroidal Anti-inflammatory Drugs (NSAIDs);

- **NSAIDs** are the ***most common*** **treatment** for **dysmenorrhea** (**first-line therapy**).
- They ***decrease*** **menstrual pain** by ***decreasing*** **intrauterine pressure** and ***lowering*** **prostaglandin F2α (PGF2α)** ***levels*** in **menstrual fluid**.
- **NSAIDs** is ***most effective*** when **therapy** is **started** ***before*** the ***onset*** of **menstrual pain** and **flow**.
- The **NSAIDs** specifically ***approved by*** the **US FDA** for ***treatment*** of **dysmenorrhea** are as *follows*:

Mefenamic Acid (Ponstel®)	500 mg initially followed by 250 mg 4 times daily; ***first choice***.
Meclofenamate (Meclomen®)	100 mg orally 3 times daily.
Diclofenac (Voltaren®)	50 mg 3 times daily.
Ibuprofen (Brufen®)	800 mg 3 times daily.
Ketoprofen (Ketofan®)	25-50 mg orally every 6 to 8 hours as needed (Max dose: 300 mg/day).
Naproxen (Naprosyn®)	500-550 mg twice daily.

- **Mefenamic acid** is also *may* ***act as*** **prostaglandins receptor *antagonist***, these effects may also be ***responsible for*** its ***effectiveness*** in the ***treatment of*** **primary dysmenorrhea** (***first choice***).
- **NSAIDs** are **used** for **short periods** to ***avoid*** **serious side effects**, including **GI bleeding** and **renal dysfunction**.
- **COX-2 inhibitor** (**Celecoxib**) is *also* ***effective*** and *may* be ***prescribed***.

B) Oral Contraceptives (OCs) and ***other*** **Hormonal Contraceptives** (***second-line*** **therapy**);

- **OCs**, which ***block*** **monthly ovulation** and *may* ***decrease*** **menstrual flow**, *may also* ***relieve*** **symptoms** by ***decrease*** **prostaglandin *production*** in the ***late*** **luteal phase**.
- **Combination OCs**, **Mini-Pill** (**Progestin Only Pill**), **Hormonal Intrauterine Device** (**Mirena®**) and **Depot Medroxyprogesterone Acetate** (**Depo-Provera®**) are ***effective*** **pain *relief*** and are *associated with* ***reduced*** **menstrual *flow***.

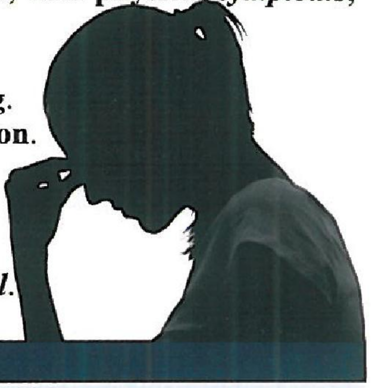
C) Other;

- ***Transdermal*** **Nitroglycerin** (a **nitric oxide *donor***) has been found ***effective*** in ***inhibiting*** **uterine contractility** and ***excellent*** **pain relief. Headache** *was* ***reported***.
- **Clonidine** *may* also **use** in **pain *relief*** in **dysmenorrhea**.

Management of Secondary Dysmenorrhea

- The ***treatment*** of **secondary dysmenorrhoea** ***depends on*** the **underlying cause**;
  - **GnRH Analogues** (**Leuprolide**) and **Danazol** *for* **endometriosis**.
  - **Antimicrobial Agents** *for* **pelvic inflammatory disease**.
- **Surgical Management** (**Laparoscopic Presacral Neurectomy**; **LPN**) *for* **chronic pelvic pain**.

Premenstrual Syndrome (PMS)



- **Premenstrual Syndrome** (PMS) is a *collection* of **emotional** *symptoms*, with **physical** *symptoms*, *related to* a **woman's menstrual cycle.**
- **PMS occurring** ***only*** *during* the **luteal phase** of the **menstrual cycle.**
- **Symptoms** ***vary between*** **women** and **resolve** ***around*** the *start* of **bleeding.**
- *Up to* **80%** of **women** *report* having ***some*** **symptoms** *prior to* **menstruation.**
- **Premenstrual Dysphoric Disorder** (**PMDD**) is a ***more*** **severe** ***form*** of **PMS** that has ***greater*** **psychological symptoms, PMDD** is *reported to* ***affect*** **3-8%** of **women.**
- ***Etiology*** of **PMS** ***remains*** **unknown** and may be ***complex*** & ***multifactorial.***
- ***Symptoms***; divided into **five basic categories; A-C-D-H-O**

Most common	Symptoms
PMS-A (Anxiety)	- Difficulty sleeping. - Tense feelings, irritability, clumsiness and mood swings.
PMS-C (Craving)	- Headache. - Cravings for sweet foods OR salty foods OR other types of food.
PMS-D (Depression)	- Depression. - Feelings of angry and violent with no reason and feelings of low self-worth. - Poor concentration or memory.
PMS-H (Hydration)	- Weight gain. - Abdominal bloating. - Breast tenderness. - Swelling of extremities.
PMS-O (Other)	- Dysmenorrhea. - Frequent urination. - Nausea. - Acne. - Upper respiratory tract infections. - Diarrhea OR Constipation. - Hot flashes or cold sweats. - General aches or pains. - Allergic reactions.

- ***Diagnosis***; *Usually*, ***no*** **laboratory test** and ***no*** **physical findings** are ***specifically*** *helpful* in ***establishing*** the ***diagnosis*** of **PMS.**
- ***Etiology***; The ***etiology*** of PMS ***remains*** **unknown** ***but*** *some* **evidence** ***suggests***;
  - A) **Hormones**;
    - **Progesterone/Estrogen** ***Imbalance***;
      - ↑ Estrogen → ↑ activity of glutamate → ↑ Excitation.
      - ↓ Progesterone → ↓ Allopregnanolone (ALLO); the main metabolite of progesterone and potent modulator of GABAA receptors → ↑ Excitation.
        (Progesterone and ALLO increase in the luteal phase and decrease quickly around menses)
    - **Aldosterone**; ↑ Aldosterone in luteal phase → fluid retention, breast tenderness & abdominal bloating.
    - **Prolactin**; ↑ Prolactin receptors in PMS → ↑ effect of Prolactin in breast tissue → Breast tenderness.
    - **Dopamine** and **Serotonin**;
      - ↓ Dopamine → ↑ prolactin.
      - ↓ Serotonin → emotional disturbances, particularly depression.
    - **Prostaglandins** ***imbalance***;
      - ↑ PGE2 → Antidiuretic and sedative effect.
      - ↓ PGE1 → Counter the action of prolactin.
  - B) **Nutritional Factors**;
    - **Vitamin B_6** ***deficiency*** (due to progesterone/estrogen imbalance); Vitamin B_6 act as co-factor in a number of enzyme reactions, leading to production of dopamine and serotonin.
    - ***Disruption*** of **Ca^{2+} homeostasis**; is *associated with* ***affective*** **disorders.**
    - ***Deficiency*** in ***essential*** **fatty acids** (**γ-linolenic acid**); Gamma-Linolenic Acid (GLA) is converted into dihomo-GLA, which form the starting point for the synthesis of PGE1.
  - C) **Psychological Factors**; Disturbance of psychological status or changes in CNS function → disrupts noradrenergic function and disrupts cerebral blood flow.

Management of Premenstrual Syndrome (PMS)

Non-Pharmacological Management

A) **Dietary *Modification***;

- ***Eating small* protein-rich meals *more* frequently (*avoid* overeating)**; 4-6 smaller meals per day.
- ***Decrease* high-sugar diet** (it has an increased risk of PMS).
- ***Restriction* of caffeine, *high* fat and salty foods.**
- ***Decrease* fluid intake**
- ***Increase* intake of natural diuretics foods**; e.g. **prunes, figs, celery** and **cucumber**.

B) ***Avoid* alcohol** and **smoking**.

C) ***Decrease* Stress**; It can *aggravate* the **symptoms** of **PMS**.

D) ***Regular* exercise**.

E) **Vitamin *supplement***;

- **Vitamin B_6**; ↓ **Mood swings, breast discomfort** and **headache**.
- **Calcium**; ↓ **Emotional** and **physical symptoms**.
- **γ-linolenic acid** (*found in* **Evening Primrose Oil**); ↓ **physical symptoms** (*especially* **breast tenderness**).
- **Vitamin E** also has shown ***some* effectiveness** (*especially* **breast tenderness**).

Pharmacological Management

A) **Oral Contraceptives**;

- **Combined Oral Contraceptive Pills (COCPs)** ***may reduce*** **physical symptoms** in ***some*** **women**, ***but do not*** *relieve* **emotional symptoms**.
- **Oral contraceptives *with* Drospirenone** (Yasmin®) are ***more* preferred**.
- **Progesterone** has been ***historically widely prescribed for*** **women** *with* **PMS**.

B) ***Other* Hormonal Therapy**;

- **Gonadotropin-releasing Hormone (GnRH) *Analogues***; can be **used** in ***severe*** *forms* of **PMS** (suppress ovulation by inhibiting the release of pituitary gonadotropins).
- **Danazol** is an **androgenic agent** that ***inhibits*** **gonadotropin release**, can be **used** in **PMS**.

C) **Antidepressants**; **SSRIs** are ***first-line treatment*** for ***severe*** **symptoms** of **PMS** and **PMDD**.

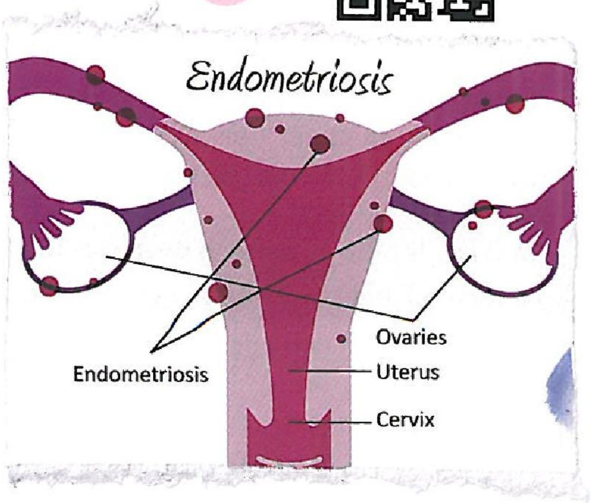
D) **Others**; - **Spironolactone** is ***effective*** in ***improving*** **symptoms** of **PMS** (*especially* **bloating**).
- **NSAIDs** and **Paracetamol** for **general pain** and **headache**.

Summary of Management Guidelines

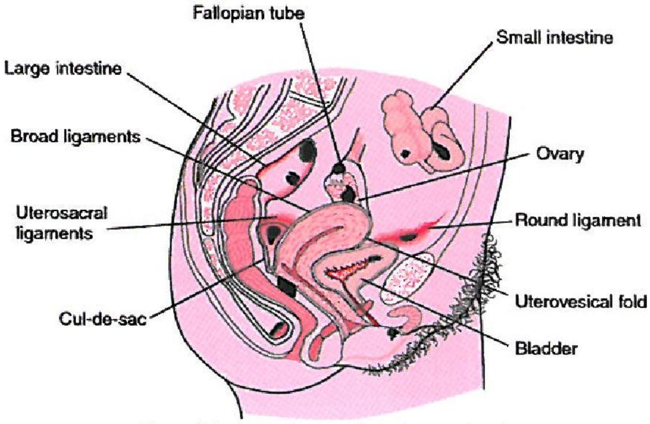
***All* women *with* PMS or PMDD**	**Non-pharmacologic Treatments** - Education, supportive therapy, rest, exercise and dietary modifications.	
Physical Symptoms	**Bloating**	- **Spironolactone.**
	Headaches	- **Paracetamol** or **Ibuprofen.**
	Fatigue and **Insomnia**	- ***Instruction*** on **good sleep hygiene.** - **Caffeine** ***restriction***.
	Breast Tenderness	- **Vitamin E, Evening primrose oil, Spironolactone** or **Danazol.**
Psychological Symptoms	- ***Continuous*** or ***intermittent*** **therapy** with an **SSRI.**	
Treatment Failure	- **Hormonal therapy** to ***manipulate*** **menstrual cycle.**	

Endometriosis

- **Endometriosis** is the ***presence*** of **normal endometrial mucosa (glands and stroma)** ***abnormally*** **implanted** in **locations** ***other than*** the **uterine cavity**.
- ***During*** **menstrual period**, ***most*** of the **uterine lining** and **blood** is ***shed*** *through* the **cervix** and into the **vagina**. *However*, ***some*** of *this* **tissue** ***enters*** the **pelvis** *through the* **fallopian tubes**, *with* ***unable*** to ***clear*** the **pelvis** of ***these*** **cells**.
- **Endometriosis** is ***typically*** seen ***during*** the **reproductive age** and ***occurs*** in *about* **6-10%** of **women**.
- The ***main*** **symptoms** are **pelvic pain** and **infertility**.



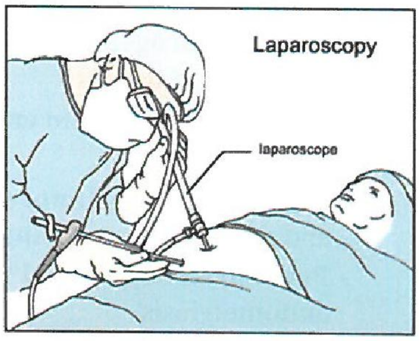
- *About* **70% pain** ***occurs*** *during* **menstruation** and is *termed* **secondary dysmenorrhoea**.
- *About* ***one third*** of **women** ***with*** **endometriosis** ***remain*** **asymptomatic**.
- **Laparoscopy** is *considered* the ***primary*** **diagnostic modality** *for* **endometriosis**.
- ***Localization*** *of* **Endometriosis**;
  - ***Most Common Sites*** (in descending order);
    - **Ovaries**.
    - ***Posterior*** **cul-de-sac**.
    - ***Broad*** **ligament**.
    - ***Uterosacral*** **ligament**.
    - ***Rectosigmoid*** **colon**.
    - **Bladder**.
    - ***Distal*** **ureter**.
  - ***Less Common Sites***; Fallopian tubes, intestines, vagina and cervix.
  - ***Rare Sites***; Lung, pleura and pericardium.



Possible locations of endometriosis

- ***Signs*** and ***symptoms*** (about one third of women with endometriosis remain asymptomatic);
  - **Infertility**; about a third of women with infertility have endometriosis.
  - **Dysmenorrhea**; painful, sometimes disabling cramps during the menstrual period; pain may get worse over time (progressive pain), also lower back pains linked to the pelvis.
  - **Chronic pelvic pain**; typically accompanied by **lower back pain** or **abdominal pain**.
  - **Heavy** or ***irregular*** **bleeding**.
  - **Dyspareunia**; painful sex.
  - **Dysuria**; urinary urgency, frequency, and sometimes painful voiding.
  - **Dyschezia** (pain on defecation); Often with cycles of diarrhea and constipation.
  - **Bloating**, **nausea** and **vomiting**.
  - **Pain** ***during*** **exercise**.
- ***Staging*** (by American Society of Reproductive Medicine); *depending on* ***location***, ***extent***, and ***depth*** of **endometriosis** ***implants***;
  - **Stage I** (**Minimal**); ***Most women***
    - Only superficial lesions and possibly a few filmy adhesions.
  - **Stage II** (**Mild**);
    - In addition, some deep lesions are present in the recto-uterine pouch (cul-de-sac).
  - **Stage III** (**Moderate**);
    - As above, plus presence of endometriomas on the ovary and more adhesions.
  - **Stage IV** (**Severe**);
    - As above, plus large endometriomas, extensive adhesions.

- ***Risk Factors***;
    - **Family history** of **endometriosis.**
    - ***Early*** **age** of **menarche.**
    - ***Short*** **menstrual cycles** (< 27 d).
    - ***Long*** **duration** of **menstrual flow** (>7 d).
    - **Heavy bleeding** ***during*** **menses.**
    - ***Delayed*** **childbearing.**
    - ***Defects*** in the **uterus** or **fallopian tubes.**
    - **Hypoxia** and **iron deficiency** may contribute to the early onset of endometriosis.
- ***Etiology***; The ***exact*** **cause** of **endometriosis** is ***unclear***, ***several*** *possible* **explanations** *include*;
    - **Retrograde Menstruation**;
        - This is the most likely explanation for endometriosis.
        - In retrograde menstruation, menstrual blood containing endometrial cells flows back through the fallopian tubes and into the pelvic cavity instead of out of the body.
        - Then grow and continue to thicken and bleed over the course of each menstrual cycle.
    - **Embryonic Cell Growth**;
        - The cells lining the abdominal and pelvic cavities come from embryonic cells.
        - When one or more small areas of the abdominal lining turn into endometrial tissue, endometriosis can develop.
    - **Surgical Scar Implantation**;
        - After a surgery, such as a hysterectomy or C-section, endometrial cells may attach to a surgical incision.
    - **Endometrial Cells Transport**:
        - The blood vessels or tissue fluid (lymphatic) system may transport endometrial cells to other parts of the body.
    - **Immunologic Dysfunction**:
        - It's possible that a problem with the immune system may make the body unable to recognize and destroy endometrial tissue that's growing outside the uterus.
    - **Genetics**;
        - Some women may have a genetic predisposition to endometriosis.
- ***Diagnosis***;
    - **Laparoscopy**; The ***only*** **way** to **confirm**;
        - Laparoscopy, a surgical procedure where a camera is used to look inside the abdominal cavity.
    - **Pelvic** ***examination.***
    - **Ultrasound, MRI** or **CT** ***examination.***
    - **CA 125** (Cancer Antigen 125): Is the only important marker in the diagnosis of stages III/IV of endometriosis.



Management of Endometriosis

Non-Pharmacological Management

A) Heat Therapy (to relax pelvic muscles);
- ***Taking*** **warm bath.**
- ***Put*** **hot water bottle** in ***lower*** **abdomen.**

B) Dietary *modifications*;
- ***Decrease*** **carbohydrate** ***intake.***
- ***Avoid*** **caffeine** ***intake***;
    - Sugar and caffeine are linked to estrogen production in the body cause hormone imbalance.
- ***Avoid*** **high** ***consumption of*** **dairy products** and **red meats**;
    - They are stimulate body production of PGs (lead exacerbate inflammation and pain).

C) Others;
- **Acupuncture**; May also be effective in the treatment of pain.

Pharmacological Management

- Medications that interrupts the normal cyclic production of reproductive hormones such as; Gonadotropin-releasing Hormone (GnRH) Agonists, Danazol, Combination Oral Contraceptive Pills (COCPs) and Progestins are currently recommended.

A) Combination Oral Contraceptive Pills (COCPs);

- **COCPs** *suppress* **LH** and **FSH;**
    - *Prevent* **ovulation.**
    - ↓ **Endometrial** *growth* and *implantation* (↓**decidualization**).
    - ↓ **Menstrual pain** *associated with* **endometriosis.**
    - ↓ **menstrual flow**
- **COCPs** or **hormonal therapy** are ***not*** a **permanent cure** *for* **endometriosis.**

B) Progestational Agents;

- **Progestins** are ***similar to*** **COCPs** in ***their*** **effects** on **FSH, LH** and **endometrial tissue.**
- **Medroxyprogesterone acetate** (**Depo-Provera®**) **is used,** ***return to*** **fertility** *may be* **delayed.**
- **Levonorgestrel Intrauterine Device** (**Mirena®**) has been *shown to* ***reduce*** **endometriosis-*associated*** **pain.**

C) Gonadotropin-releasing Hormone (GnRH) Analogues;

- These **drugs** are thought to ***work by decreasing*** **hormone levels.**
- **Goserelin** (**Zoladex®**) and **Leuprolide** (**Lupron®**) are the ***commonly*** **used.**
- **GnRH Analogues** ***improve*** **pain** *associated with* **endometriosis.**
- **Calcium** ***supplementation*** are ***recommended*** to ***reduce*** the ***loss*** of **bone density** that ***occurs*** with ***therapy.***

D) Danazol and Gestrinone;

- They acts by ***inhibiting*** the ***mid-cycle*** **FSH** and **LH** ***surges*** and ***preventing*** **steroidogenesis** in the **corpus luteum.**
- They are ***less*** **frequently used** to ***treat*** **endometriosis today** (GnRH analogues are equally effective and have a more favorable side-effect).
- ***Highly*** **androgenic side effects; acne, hirsutism,** ***deepening*** **voice** and **male pattern baldness.**

E) Aromatase Inhibitors;

- **Evidence** is ***limited*** in **endometriosis** due to the limited number and quality of studies available.

F) Others;

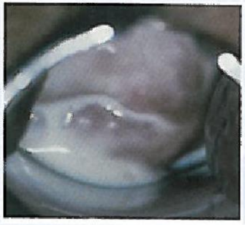
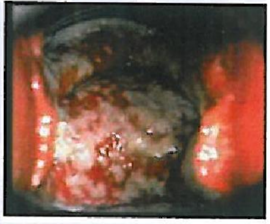
- **NSAIDs** (such as **Ibuprofen** or **Naproxen**) are ***commonly*** **prescribed** to *help* ***relieve*** **pelvic pain** and **menstrual cramping.**
- **Pentoxifylline** (**Trental®**) may ***improve*** **pain** as well as ***improve*** **pregnancy rates** in **women** *with* **endometriosis.**

Surgical Management

- **Surgical treatment** is the ***preferred*** approach to **infertile patients** with ***advanced*** **endometriosis.**
- *After* **surgery, medical therapy** *may* be **needed** to ***control*** **symptoms** of **endometriosis** (recurrent pain symptoms within two years of surgery).
- **Surgical therapies** for **endometriosis** may be either ***classified into***:
    - **Conservative surgery**; In which the **uterus** and **ovarian tissue** is ***preserved.***
    - **Definitive surgery**; ***Involves*** **hysterectomy** (*removal of* the **uterus**), ***with*** or ***without*** **removal** of the **ovaries.**

Vaginitis

- **Vaginitis** is ***inflammation*** of the **vagina**.
- **Vulvovaginitis**, is an ***inflammation*** of the **vagina** and **vulva**.
- D*iagnosis based on* ***presence*** of ***abnormal*** **discharge, vulvovaginal discomfort** (**irritation**) or **both**.
- It is ***usually*** *due to* **infection; bacterial vaginosis** is the ***most common*** **vaginal infection**.
- ***Normal*** **discharge** is *usually* **clear** or **milky** *with* ***no*** **malodor**.
- ***Most Common Symptoms***;
  - **Irritation** or **itching** of the **genital area**.
  - ***Abnormal*** **vaginal discharge** *with* an **unpleasant odor**.
  - **Burning** *during* **urination**.
  - **Discomfort** *during* **sexual intercourse**
- ***Types*** of **Vaginitis**;
  1) **Bacterial vaginosis**; Which results from overgrowth of one of several organisms normally present in vagina.
  2) **Vulvovaginal Candidiasis**; Which are usually caused by a naturally occurring fungus called *Candida*.
  3) **Trichomoniasis**; Which is caused by a parasite and is commonly transmitted by sexual intercourse.
  4) **Atrophic Vaginitis** (non-infectious vaginitis); Which results from reduced estrogen levels after menopause

	1) Bacterial Vaginosis (BV)	**2) Vulvovaginal Candidiasis (VVC)**
Normally	- A ***healthy*** **vagina** ***normally*** **contains** *many* **microorganisms**, *if* the **balance** of **microorganisms** is ***disrupted*** → lead to **bacterial** or **yeast** ***infection***.	
Causes	- ***Decrease*** **growth** of ***Lactobacillus***. - ***Overgrowth*** of a **bacterial organisms** *usually* ***Gardnerella vaginalis***, ***Mobiluncus***, ***Bacteroides***, and ***Mycoplasma hominis***.	- ***Overgrowth*** of a **fungal organisms** *usually* ***Candida albicans***.
Incidence	- ***Most common*** in **childbearing age**.	- ***Most common*** in **reproductive age**.
Risk Factors	- ***New/multiple*** **sex partners**. - **Natural** ***lack*** of **lactobacilli**. - **Smoking**. - **Vaginal douching** (upsets the natural balance of vaginal environment). - **Uses** of **intrauterine device** (**IUD**). - *Frequent use* of *higher doses* of **spermicide nonoxynol-9**	- **Antibiotics use**. - ***Increased*** **estrogen levels**. - ***Uncontrolled*** **diabetes**. - **Diet** ***high*** in **refined sugars**. - ***Impaired*** **immune system**. - **Sexual activity**. - **Uses** of **intrauterine device** (**IUD**).
Clinical Features	1) **Discharge appearance**; * Off-white discharge. * Thin & homogenous. * Foul-smelling "fishy" vaginal odor.  2) **Symptoms**: - *Usually* ***without*** *significant*; - **Irritation** or - **Erythema**	1) **Discharge appearance**: * Little/No discharge, *if present*; * White & clumpy. * Thick * Cottage cheese appearance.  2) **Symptoms**: - **Itching** and **irritation**. - **Redness** and **swelling** of the **vulva**. - **Vaginal pain** and **soreness**. - **Dysuria** and **dyspareunia**.
Diagnosis	- **Discharge appearance** - **Vulva appearance** - **pH** *of* **discharge; > 4.5** - **Microscopically** - **Whiff amine test** (vaginal discharge + 10% KOH); **fishy odor** (+ve).	- **Discharge appearance** - **Vulva appearance** - **pH** of **discharge**; *typically* 4-4.5 - **Microscopically** - **Whiff amine test** (vaginal discharge + 10% KOH); ***absence*** of **fishy odor** (-ve).
Complications	- **Preterm birth**. - ***Increase*** **risk** of **sexually transmitted infections** *such as* **HIV**.	- It is also **complicated** *if*; **pregnant**, ***uncontrolled*** **diabetes**, ***poor*** **immune function**.

Treatment of Bacterial Vaginosis (BV)

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (CDC).
    - *Non-pregnant women*;
        - **Metronidazole** 500 mg orally twice daily for 7 days.
        - OR **Clindamycin** 2% cream, 1 full applicator intravaginally at bedtime for 7 days.
        - OR **Metronidazole** 0.75% gel one full applicator intravaginally once daily for 5 days.
        - *Alternatives*:
            - **Clindamycin** ovules 100 mg intravaginally at bedtime for 3 days.
            - OR **Clindamycin** 300 mg orally twice daily for 7 days.
            - OR **Tinidazole** 2 g orally once daily for 2 days.
            - OR **Tinidazole** 1 g orally once daily for 5 days.
    - *Pregnant women*;
        - **Metronidazole** 500 mg orally twice daily for 7 days.
        - OR **Metronidazole** 250 mg orally three times daily for 7 days.
        - OR **Clindamycin** 300 mg orally twice daily for 7 days.
- ***Do not*** **use Clindamycin** *cream* ***during*** **pregnancy** because of the ***increased*** **risk** of **preterm deliveries**.
- **Treatment** of **sexual partners** is ***not*** **necessary**.

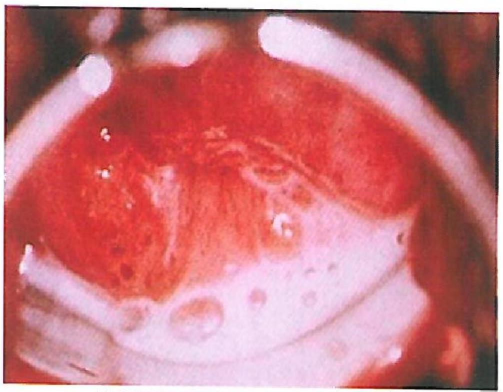
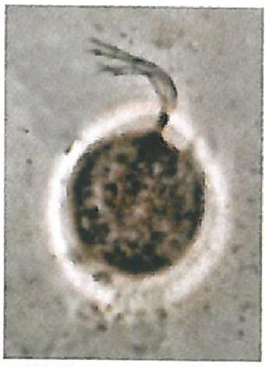
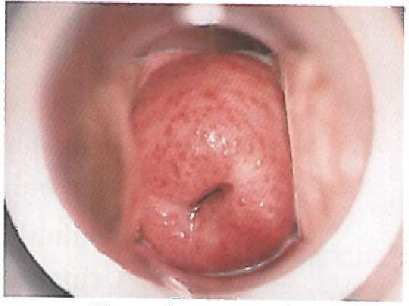
Treatment of Vulvovaginal Candidiasis (VVC)

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention** (CDC).
    - ***Therapeutic Regimens***;

Drug	Dose	Length of Therapy
Butoconazole	2% cream: 5 g intravaginally	1 dose
Clotrimazole	1% cream: 5 g intravaginally at bedtime	7–14 days
	2% cream: 5 g intravaginally at bedtime	3 days
Miconazole	2% cream: 5 g intravaginally at bedtime	7 days
	4% cream: 5 g intravaginally at bedtime	3 days
	100-mg vaginal suppository at bedtime	7 days
	200-mg vaginal suppository at bedtime	3 days
	1200-mg vaginal suppository	1 dose
Nystatin	100,000-unit vaginal tablet at bedtime	14 days
Terconazole	0.4% cream: 5 g intravaginally at bedtime	7 days
	0.8% cream: 5 g intravaginally at bedtime	3 days
	80-mg vaginal suppository at bedtime	3 days
Tioconazole	6.5% ointment: 5 g intravaginally	1 dose
Fluconazole	150-mg oral tablet	1 dose

- ***Recurrent*** **vulvovaginal candidiasis** (**four** or ***more*** **episodes** a **year**);
    - ***Longer*** **duration** of **initial therapy**;
        - **7–14 days** of **topical therapy**.
        - 100-150 or 200mg oral dose of **Fluconazole** ***every*** **third day** for a total of **3 doses**.
    - ***Maintenance regimen***; Oral **Fluconazole** 100, 150, or 200 mg/week for 6 months.
- ***Pregnant women***; ***Drugs of choice*** is **topical azole**, *applied for* **7 days**.
- **Home remedies** for ***recurrent*** **vulvovaginal candidiasis**;
    - ***Daily*** **intake** of **yogurt** (*containing* **live** ***Lactobacillus acidophilus***).
    - ***Eliminate*** **use** of **nylon** or **tight-fitting clothing**.
    - **Consider** ***discontinuing*** **oral contraceptive**.
    - ***Improve*** **glycemic control** in **diabetic patient**.

3) Trichomoniasis (*Trichomonas vaginalis*)

Definition	- **Trichomoniasis** is a ***sexually transmitted*** **infection** that in **women** can cause a ***foul-*****smelling vaginal discharge, genital itching** and **painful urination.** - **Men** who have **trichomoniasis** ***typically*** have **no symptoms.** - **Pregnant women** who have **trichomoniasis** are at ***higher risk*** of **delivering prematurely.**
Causes	- ***Trichomonas vaginalis***; is an **anaerobic, flagellated protozoan**, a form of **microorganism.**
Incidence	- The **worldwide prevalence** of **trichomoniasis** is **174 million**; these cases account for **10-25%** of ***all*** **vaginal infections.**
Risk Factors	- ***Having*** **multiple sexual partners.** - ***History*** of ***other*** **sexually transmitted diseases.** - ***Previous*** **episode** of **trichomoniasis.**
Clinical Features	1) **Discharge appearance**; * **Profuse, frothy** and **watery** (**Thin**). * **Malodorous.** * **Yellow-green discharge.** 2) **Symptoms**; - **Itching** and **irritation.** - **Redness** and **swelling** of the **vulva.** - **Vaginal pain** and **soreness.** - **Dysuria** and **dyspareunia** 
Diagnosis	- **Discharge** ***appearance.*** - **Vulva** ***appearance.*** - **Strawberry cervix.** - **pH** of **discharge**; 5-7. - **Microscopically**; - **Flagellate protozoa.** - **Highly motile.** - **Pear shaped.**  *Trichomonas vaginalis*  ***Strawberry cervix*** (due to capillary dilation as a result of the inflammatory response)
Complications	- **Preterm delivery.** - ***Low*** **birth weight.** - ***Increase*** **predisposing** to **AIDS.**

Treatment of Trichomoniasis

- **Treatments**; **2015 STDs Guidelines** *from* **Centers** for **Disease Control** and **Prevention (CDC)**.
  - **Metronidazole** 2 g orally in a ***single dose*** OR **Tinidazole** 2 g orally in a ***single dose.***
  - ***Alternative***; **Metronidazole** 500 mg orally twice daily for 7 days.
- ***All sexual*** **partners** *should be* **treated.**

4) Atrophic Vaginitis (Vaginal Dryness)

Definition	- **Atrophic vaginitis** is an ***inflammation*** of the **vagina** due to the ***thinning*** and ***shrinking*** of the **tissues**, as well as ***decreased*** **lubrication** (***non*-infectious vaginitis**).
Causes	- **Vaginal atrophy** is *caused by* ***decrease*** in **Estrogen** ***production***. - *Less* **Estrogen** makes **vaginal tissues** ***thinner***, ***drier***, ***less*** **elastic** and ***more*** **fragile**.
Risk Factors	- ***After*** **menopause**. - ***Other conditions*** *associated with* **estrogen** ***deficiency***. - **Oophorectomy** (surgical removal of ovaries). - **Radiation therapy**. - **Chemotherapy**. - **Immunologic disorders**. - **Premature ovarian** ***failure***. - **Endocrine disorders**. - **Antiestrogen medications**.
Clinical Features	1) **Discharge appearance**; - ***No*** **abnormal discharge**. 2) **Symptoms**; - **Vaginal dryness** and **burning**. - **Dysuria** (burning with urination). - **Dyspareunia** (painful sexual intercourse). - ***More*** **urinary tract infections**. - ***Light*** **bleeding after intercourse**. - ***Decreased*** **vaginal lubrication** ***during*** **sexual activity**.
Diagnosis	- **Pelvic examination** and **appearance**. - **Urine test**. - **Acid balance test**.
Complications	- **Vaginal** ***infections*** - **Urinary** ***problems***.

Management of Atrophic Vaginitis

A) Hormone Replacement Therapy (HRT);

- ***All*** **routes** of **Estrogen delivery** ***relieve*** the **symptoms** of **atrophic vaginitis**.

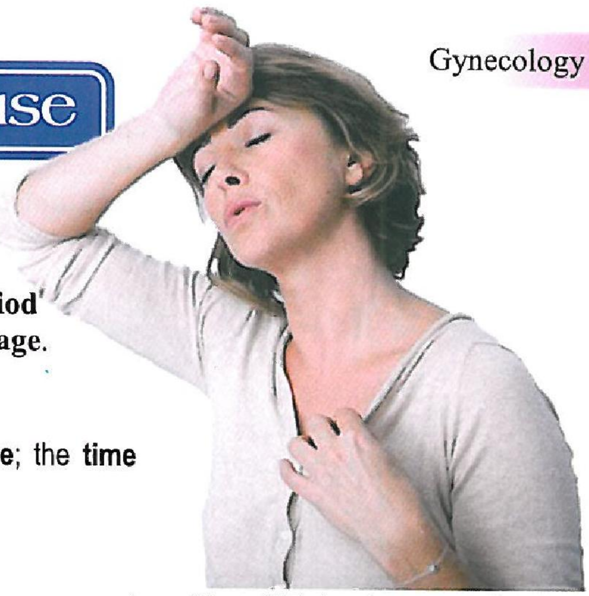
B) Vaginal Lubricant (**K-Y® gel**);

- ***Reduce*** **discomfort** ***during*** **sexual intercourse**.

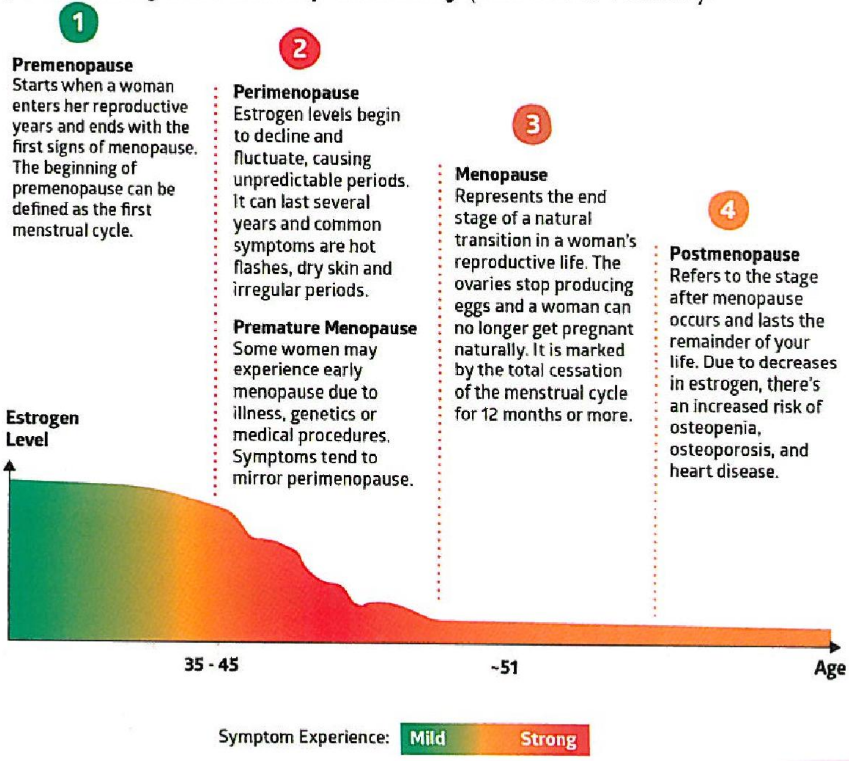
C) Vaginal Moisturizer (**Replens®**);

- ***Restore*** *some* **moisture** to **vaginal area**.

Menopause



- **Menopause** *literally means* the **"end of monthly cycles"**.
- **Menopause** is the ***permanent*** **end of menstruation** (**amenorrhea**) and **fertility**.
- ***Defined as occurring*** **12 months** *after* ***last*** **menstrual period**
- **Menopause** ***typically*** occurs *between* **49** and **52 years** of **age**.
- **Premenopause** (*before* menopause);
  - The term "**pre**" means "**before**"
  - **Premenopause**; ***any time*** *before* she **enters menopause**; the **time** ***between*** a **woman's first** and **last period**.
- **Perimenopause** (***around*** menopause);
  - The term "**peri**" means "**surrounding**" or "**near**".
  - **Perimenopause**; **time of** *transition* ***towards*** **menopause** (**menopause transition; MT**); begins ***several*** **years** ***before*** **menopause** (4-8 years) with **hormonal changes** and *presence of* **clinical symptoms** (**Hot flashes**, **insomnia**, **weight gain** and **bloating**, **mood** ***changes***, **headache** and ***irregular*** **menses**).
- **Postmenopause** (***after*** menopause);
  - The term "**post**" means "**after**"
  - **Postmenopause**; **describes women** who have ***not*** **experienced** ***any*** **menstrual flow** for a ***minimum*** of **12 months**.
- ***Causes*** of **Menopause**;
  - A) **Age** (**natural** ***decline of*** **reproductive hormones**);
    - **Menopause** ***typically*** occurs *between* **49** and **52 years** of **age**.
    - In **40s**, **menstrual periods** may ***become*** **longer** *or* **shorter**, **heavier** *or* **lighter**, and ***more*** *or* ***less*** **frequent**, ***until*** **ovaries** ***stop*** **producing eggs**, and have ***no more*** **periods** (**amenorrhea**).
  - B) **Premature Ovarian Failure** (**POF**);
    - **POF** is the ***cessation*** of the **ovarian function** ***before*** the **age** of **40 years**.
    - ***Causes*** of **POF** *include* **autoimmune disorders**, **thyroid disease**, **diabetes mellitus**, **chemotherapy**, *being* a **carrier** of the **fragile X syndrome gene**, and **radiotherapy**.
    - ***Early*** **menopause** can be *related to* **cigarette smoking**, ***higher*** **body mass index**, **racial** and **ethnic factors** and **illnesses**.
  - C) **Surgical Menopause**;
    - **Menopause** can be **surgically** ***induced by*** **bilateral oophorectomy** (*removal of* **ovaries**).
    - ***Removal*** of the **uterus** ***without*** **removal** of the **ovaries** (***partial*** **hysterectomy**) ***does not*** **directly** *cause* **menopause**, *but* can **precipitate** ***earlier*** **menopause**.
- ***Physiology***;
  - The **menopausal transition**, and **postmenopause** ***itself***, is a **natural change**, ***not*** usually a **disease state** or a **disorder**.
  - The ***main*** **cause** of this ***transition*** is the ***natural*** **depletion** and **aging** of the **finite amount** of **oocytes** (**ovarian reserve**).
  - The ***depletion*** of the **ovarian reserve** causes an ***increase*** in ***circulating*** **FSH** and **LH**.



Premenopause
Starts when a woman enters her reproductive years and ends with the first signs of menopause. The beginning of premenopause can be defined as the first menstrual cycle.

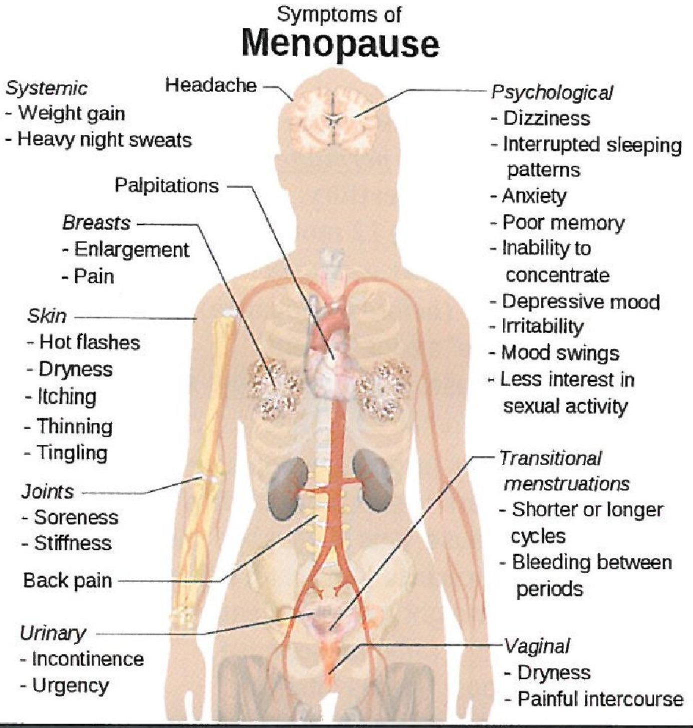
Perimenopause
Estrogen levels begin to decline and fluctuate, causing unpredictable periods. It can last several years and common symptoms are hot flashes, dry skin and irregular periods.

Premature Menopause
Some women may experience early menopause due to illness, genetics or medical procedures. Symptoms tend to mirror perimenopause.

Menopause
Represents the end stage of a natural transition in a woman's reproductive life. The ovaries stop producing eggs and a woman can no longer get pregnant naturally. It is marked by the total cessation of the menstrual cycle for 12 months or more.

Postmenopause
Refers to the stage after menopause occurs and lasts the remainder of your life. Due to decreases in estrogen, there's an increased risk of osteopenia, osteoporosis, and heart disease.

- ***Signs*** and ***Symptoms***;
  - ***During*** the **menopausal transition** (**MT**) and **after menopause**, **women** can ***experience*** a ***wide range*** of **symptoms**.
  - ***Most common*** **symptoms**;
    1) **Vasomotor Symptoms** (**VMS**);
       - **Hot flashes.**
       - **Night sweats.**
       - **Palpitations.**
       - **Mood changes.**
       - **Depression** and **anxiety.**
    2) **Vulvovaginal Atrophy** (**VVA**);
       - **Vaginal dryness** and **vaginal burning.**
       - **Dysuria** (burning with urination).
       - **Dyspareunia** (painful intercourse).
       - ***More*** **urinary tract infections.**
       - ***Light*** **bleeding after intercourse.**
    3) **Osteoporosis**;
       - ***Increased*** **risk** of **bone fractures.**


Symptoms of
Menopause
Systemic
- Weight gain
- Heavy night sweats
Headache
Palpitations
Breasts
- Enlargement
- Pain
Skin
- Hot flashes
- Dryness
- Itching
- Thinning
- Tingling
Joints
- Soreness
- Stiffness
Back pain
Urinary
- Incontinence
- Urgency
Psychological
- Dizziness
- Interrupted sleeping patterns
- Anxiety
- Poor memory
- Inability to concentrate
- Depressive mood
- Irritability
- Mood swings
- Less interest in sexual activity
Transitional menstruations
- Shorter or longer cycles
- Bleeding between periods
Vaginal
- Dryness
- Painful intercourse

1) Vasomotor Symptoms (VMS)

- **Hot flashes** (**HFs**) are the ***most common*** **symptom**.
- **Night sweating** is ***generally*** *reported in* the **face**, **neck** and **chest**.
- **Estrogen** ***withdrawal*** *lead to* ***increase*** **central sympathetic activity** (***increase*** **brain norepinephrine**) → ↑ ***activation*** of **central α₂-receptors** in **thermoregulatory center** → **vasodilatation** → **heat loss** → **hot flashes** and **sweating**.
- **Estrogen** ***withdrawal*** **theory** ***supports*** the **mood symptoms** and **depression** in **perimenopausal** and **menopausal women**.
- **Estrogen** affects **brain levels** and **metabolism** of **neurotransmitters** such as **dopamine**, **norepinephrine**, **β-endorphin** and **serotonin**; ***all*** of which can ***affect*** **emotional pathways**.

Management of Vasomotor Symptoms (VMS)

Non-Pharmacological Management

A) **Lifestyle Changes**;
- **Layered clothing**;
  - Wear light layers of clothes with natural fibers such as cotton.
  - Make sure all layers are light colors and breathable fabrics.
- **Cool atmosphere**;
  - Make sure windows are cracked open wherever sit.
  - Keep the fans or air conditioner on with proper ventilation.
- **Cool drinks** and **avoiding hot/spicy food**;
  - Drinking cool liquids, and avoiding triggers such as hot/spicy food can help with the severity of hot flushes.
- **Exercise/weight loss**;
  - Regular exercise and weight loss may help in relieving VMS.
- **Smoking cessation**;
  - Smoking cessation can help reduce VMS.

B) **Acupuncture**; acupuncture can help to improve in VMS and quality of life.

C) **Others**; hypnosis, yoga and massage can help reduce VMS.

Pharmacological Management

A) Estrogen Hormone Therapy;

- **Estrogen replacement therapy** ***remains*** the ***most effective*** **treatment** for **VMS.**
- *Increased* **risk** of **breast** and **endometrial cancer** and **cardiovascular disease.**
- *Current recommendations* to *control* **menopausal symptoms** are to **use hormone replacement therapy** at the ***lowest*** **effective dose** for the ***shortest*** **duration** of **time.**
  - ***Transdermal*** **patches** *of* **Estrogens** (Sandoz® Estradiol Derm) (Fem 7®) ***more*** **preferred.**
  - ***Oral*** and ***vaginal*** **cream** *of* **Conjugated Estrogens** (Premarin®), ***vaginal*** **ring** *of* **Estradiol acetate** (Femring®) and ***vaginal*** **tablet** of **Estradiol hemihydrate** (Vagifem®) are also ***commonly*** **used.**

B) Non-estrogen Hormone Therapy;

1) Progestins;

- ***Oral*** **Medroxyprogesterone Acetate** (Provera®) and **Megestrol Acetate** (Megace®) are ***sometimes*** used to ***counteract*** **hot flashes.**
- ***Increased*** **risk** of **bone loss.**

2) Tibolone (Livial®);

- **Tibolone** is a **Selective Tissue Estrogenic Activity Regulator (STEAR)**; it is ***possesses*** a **complex pharmacology** and has ***weak*** **estrogenic, progestogenic** and **androgenic** ***activity.***
- **Tibolone** is ***approved for*** use in **many countries** *but* ***not*** in the **United States.**
- It is **used** in **menopausal hormone therapy;** ***reduces*** **hot flashes,** ***prevents*** **bone loss** and ***improves*** **vaginal atrophy.**
- **Tibolone** is also ***used*** in **endometriosis.**
- ***Common side effects***; **Headache, weight gain** and **uterine bleeding.**

C) Non-Hormone Therapy;

1) Antidepressants;

- **Selective Serotonin Reuptake Inhibitors (SSRIs)** *such as* **Paroxetine** (Seroxat®) and **Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)** *such as* **Venlafaxine** (Effexor®) have been appeared to be ***effective*** in ***reducing*** **VMS.**

2) Anticonvulsants;

- **Gabapentin** (Neurontin®); have been **used** for the ***treatment*** of **VMS.**

3) Centrally α_2 adrenergic Agonist;

- **Clonidine** (Catapres®) **patch; Clonidine** ***reduces*** **central sympathetic** ***activation*** and ***reduces*** **VMS.**

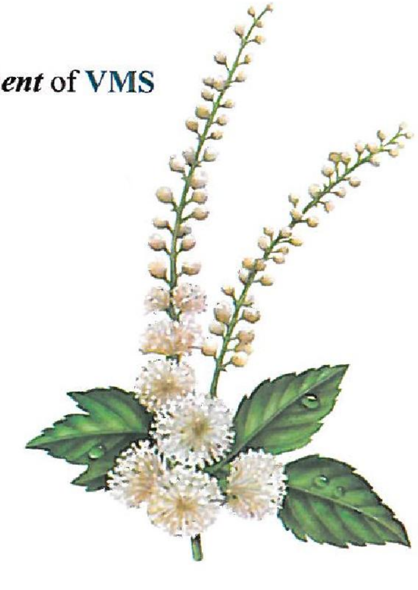
D) Phytotherapy and Supplements;

1) Phytoestrogens;

- **Soy Isoflavones** (PHYTO SOYA®); *may* **useful** in ***treatment*** of **VMS** *such as* **hot flashes, night sweats** and **anxiety.**
  - Soy Isoflavones are bioflavonoids found in soy products.

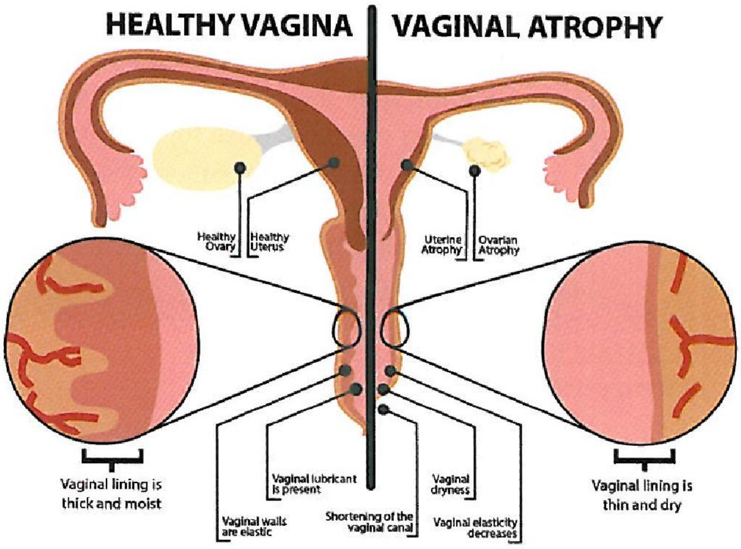
2) Non-Phytoestrogens;

- **Black Cohosh** (*Actaea racemosa*);
  - ***Improve*** **VMS** and *symptoms of* **depression.**
- **Dehydroepiandrosterone (DHEA)** ***supplements***;
  - *May* ***decrease*** **hot flashes.**
- **Ginseng;**
  - *May* ***improve*** **mood.**
- **Valerian;**
  - ***Improves*** **sleep disorders (insomnia).**
- **Vitamin E:**
  - *May* ***decrease*** **hot flashes.**



Black Cohosh

2) Vulvovaginal Atrophy (VVA)


HEALTHY VAGINA
VAGINAL ATROPHY
Healthy Ovary
Healthy Uterus
Uterine Atrophy
Ovarian Atrophy
Vaginal lining is thick and moist
Vaginal lubricant is present
Vaginal walls are elastic
Shortening of the vaginal canal
Vaginal dryness
Vaginal elasticity decreases
Vaginal lining is thin and dry

- The **symptoms** of **Vulvovaginal Atrophy** (**VVA**) *such as* **vaginal dryness, irritation, itching, dysuria** and **dyspareunia**, are *caused by loss* of **estrogen** ***production*** with **menopause**.
- As **estrogen levels** ***decrease***, the **vulvovaginal tissue** *becomes*;
  - Progressively avascular.
  - Collagen fibers fuse and hyalinize.
  - Fragmentation of elastic fibers.
  - Increases connective tissue.
  - Thin of vaginal epithelium.
  - Shortening and narrowing of the vagina (due to loss of elasticity).
  - Decreased vaginal secretions (due to limited blood flow).

Management of Vulvovaginal Atrophy (VVA)

A) **Hormone Replacement Therapy** (**HRT**);
  - ***All*** **routes** of **Estrogen delivery** ***relieve*** the **symptoms** of **atrophic vaginitis**.

B) **Vaginal Lubricant** (**K-Y$^{®}$ gel**); ***Reduce*** **discomfort** ***during*** **sexual intercourse**.

C) **Vaginal Moisturizer** (**Replens$^{®}$**); ***Restore*** *some* **moisture** to **vaginal area**.

3) Osteoporosis

- **Osteoporosis** is **one** of the ***most pervasive*** **conditions** in **older women**.
- The ***onset*** of **menopause** *leads to* ***rapid*** **loss** of **bone mineral density** (**BMD**).
- **Bone mineral density** ***screening*** ***should*** ***be*** **performed** in ***all*** **women** ***older than*** **65 years**.

[Osteoporosis was fully discussed in bone and joint chapter]

Management of Osteoporosis

Non-Pharmacological Management

A) **Diet** and **Supplements**;
  - **Calcium** and **Vitamin D**; ***All*** **postmenopausal women** ***should*** have ***adequate*** **intake** of **Calcium** and **Vitamin D** to ***maintain*** **bone health**.
  - **Femarelle$^{®}$** is a **dietary supplement** that is a *mixture of* **DT56a** (a **tofu extract**) and **flaxseed powder**, that may act as a **selective estrogen receptor modulator** (**SERM**).
  - **Soy Isoflavones** have ***potential*** **bone protective** ***effects***.

B) ***Limit*** **Alcohol**, **Phosphorus** (carbonated beverages), **Caffeine** and **Sodium** ***intake***.

C) ***Exercise***; can ***decrease*** the **risk of falls**.

Pharmacological Management

A) **Bisphosphonates** *such as*; **Alendronate**, **Etidronate**, **Ibandronate**, **Risedronate** and **Zoledronic Acid** are ***potent*** **bone resorption inhibitors** and ***remain*** **first-line** ***treatment***.

[Don't forget → Bisphosphonates Precautions]

B) **Selective Estrogen Receptor Modulators** (**SERMs**) *such as*; **Raloxifene** (**osteoporosis**) and **Bazedoxifene/Conjugated Estrogens** (**osteoporosis** and **VMS**).

C) **Selective Tissue Estrogenic Activity Regulator** (**STEAR**); **Tibolone** (**osteoporosis, VMS & VVA**).

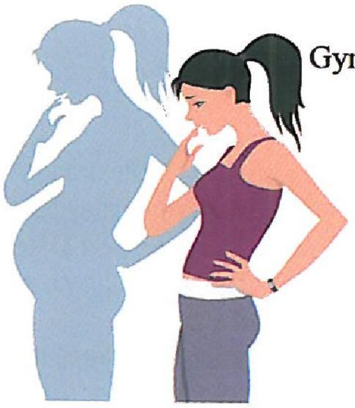
D) **Calcitonin**; is a **peptide hormone** that acts by inhibiting osteoclasts, which are involved in bone resorption

E) **Denosumab** (Prolia$^{®}$); is a **monoclonal antibody** with affinity for nuclear factor-kappa ligand (RANKL).

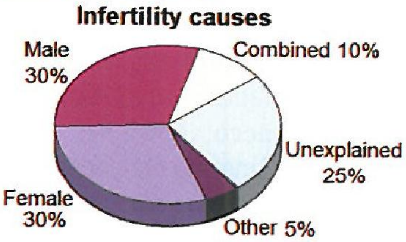
F) **Teriparatide** (Forteo$^{®}$); is a ***recombinant form*** of **human parathyroid hormone** (**PTH**).

G) **Hormone Replacement Therapy** (**HRT**); **Estrogen therapy** ***considered*** a **second-line therapy**.

Infertility

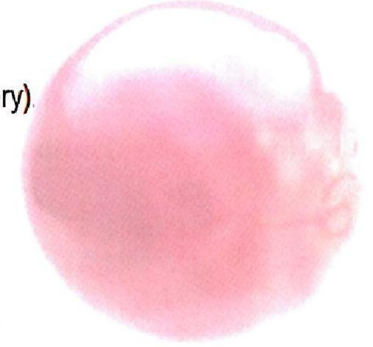


- **Infertility** is *defined as* **not being** able *to* **get pregnant (conceive)** ***after*** **one year** (or ***longer***) of ***unprotected*** **sex.**
- **Infertility affects** *approximately* **10-15%** of **reproductive-aged *couples*.**
- **Secondary infertility** is ***failure*** to **conceive** *following* a ***previous*** **pregnancy.**
- **Causes** of **Infertility**;
  - **Unexplained.**
  - **Female factors.**
  - **Male factors.**
  - **Combined.**
  - **Other.**



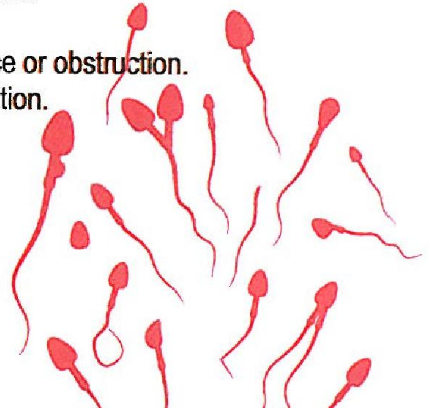
A) Female Factors;

1) **Ovulation Disorders** (40%);
   - Aging.
   - Diminished ovarian reserve.
   - Endocrine disorder (hypothalamic amenorrhea, hyperprolactinemia, thyroid disease, adrenal disease).
   - Polycystic ovary syndrome (PCOS).
   - Premature ovarian failure (POF).
   - Tobacco use.
2) **Tubal Factors** (30%);
   - Obstruction (e.g., history of pelvic inflammatory disease, tubal surgery).
3) **Endometriosis** (15%).
4) **Other** (about 10%).
5) **Uterine/cervical Factors** (> 3%);
   - Congenital uterine anomaly.
   - Fibroids and Polyps.
   - Poor cervical mucus quantity/quality (caused by smoking, infection).
   - Uterine synechiae.



B) Male Factors;

1) **Unknown** (40-50%).
2) **Primary hypogonadism** (30-40%);
   - Androgen insensitivity.
   - Congenital or developmental testicular disorder (e.g., Klinefelter syndrome).
   - Medication (e.g., alkylating agents, antiandrogens, cimetidine, ketoconazole, spironolactone).
   - Orchitis, including mumps orchitis.
   - Radiation.
   - Testicular trauma.
   - Cryptorchidism
   - Systemic disorder.
   - Varicocele.
   - Y chromosome defect.
3) **Altered sperm transport** (10-20%)
   - Absent vas deferens or obstruction.
   - Erectile dysfunction.
   - Epididymal absence or obstruction.
   - Retrograde ejaculation.
4) **Secondary hypogonadism** (1-2%)
   - Androgen excess state (e.g., tumor, exogenous administration).
   - Congenital idiopathic hypogonadotropic hypogonadism.
   - Estrogen excess state (e.g., tumor).
   - Infiltrative disorder (e.g., sarcoidosis, tuberculosis).
   - Medication effect.
   - Multiorgan genetic disorder (e.g., Prader-Willi syndrome).
   - Pituitary adenoma.
   - Trauma.



- **Risk Factors**;
    - **Age**;
        - A woman's fertility gradually declines with age and this decline becomes more pronounced in mid-30s.
        - Men over age 40 may be less fertile than younger men.
    - **Sexually Transmitted Diseases (STDs)**;
        - STDs can lead to pelvic inflammatory disease (PID) in women, and epididymitis in men.
    - **Emotional Factors**;
        - Depression and stress may have a direct effect on the hormones that regulate reproduction and affect sperm production or ovulation.
    - **Occupational** and **Environmental Risks**;
        - Studies suggest that prolonged exposure to high mental stress, high temperatures, chemicals and radiation may reduce fertility in both men and women
    - **Tobacco**;
        - Smoking can increase the risk of erectile dysfunction and low sperm count in men.
        - Smoking also reduces the possible benefit of fertility treatment.
    - **Alcohol**:
        - Alcohol use increases the risk of birth defects, and it may also make it more difficult to become pregnant.
        - Heavy alcohol use can decrease sperm count and motility.
    - **Overweight**;
        - Women overweight may increase the risk of infertility.
        - Man's sperm count may be affected if he is overweight.
    - **Underweight**;
        - Women at risk of fertility include those with eating disorders, such as anorexia.
    - **Lack of Exercise**;
        - Lack of or not enough exercise contributes to obesity.
- **Diagnosis**;

A) **Infertility Evaluation** in **Men**;

1) **History**;

- Coital practices.
- Developmental history.
- Medical history (e.g., genetic disorders, chronic illness, genital trauma, orchitis).
- Medications (e.g., sulfasalazine, methotrexate, colchicine, cimetidine, spironolactone).
- Previous fertility.
- Recent high fever.
- Substance use.
- Surgical history (previous genitourinary surgery).
- Toxin exposure.
- Potential sexually transmitted disease exposure.

2) **Physical Examination**;

- Genital infection (discharge, prostate tenderness)
- Hernia.
- Presence of vas deferens.
- Testicular mass.
- Signs of androgen deficiency (e.g., increased body fat, decreased muscle mass, decreased facial and body hair, small testes, Tanner stage < 5).
- Varicocele.

3) **Laboratory Evaluation/Specialized Tests**;

- Semen analysis (two or more samples).
- Complete blood cell count (if infection suspected).
- Post-ejaculatory urinalysis (if retrograde ejaculation).
- Follicle-stimulating hormone, testosterone levels (if hypogonadism suspected).
- Gonorrhea and chlamydia cultures, urinalysis (if genital infection suspected).
- Other laboratory studies based on history and physical examination findings.
- Specialized sperm studies (if initial evaluation of both partners unrevealing).
- Transrectal ultrasonography (if ejaculatory duct obstruction suspected).
- Renal and liver function studies.
- Scrotal ultrasonography.

WHO 1999 Seminal Fluid Analysis Reference Values

- **Volume**; More than 2 mL.
- **Sperm concentration**; More than 20 million per mL.
- **Total sperm number**; More than 40 million per ejaculate.
- **Sperm motility**; More than 50% motile and/or more than 25% progressively motile.
- **Sperm morphology**; More than 14% normal forms using strict criteria.

B) Infertility Evaluation in **Women**;

1) History;

- Coital practices.
- Medical history (e.g., genetic disorders, endocrine disorders, history of pelvic inflammatory disease)
- Medications (e.g., hormone therapy).
- Menstrual history.
- Potential sexually transmitted disease exposure, symptoms of genital inflammation (e.g., vaginal discharge, dysuria, abdominal pain, fever).
- Previous fertility.
- Substance use, including caffeine.
- Surgical history (previous genitourinary surgery).
- Toxin exposure.

2) Physical Examination;

- Breast formation and Galactorrhea.
- Genitalia (e.g., patency, development, masses, tenderness, discharge).
- Signs of hyperandrogenism (e.g., hirsutism, acne, clitoromegaly).

3) Laboratory Evaluation/Specialized Tests;

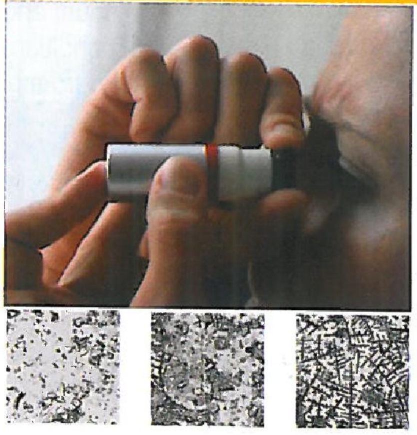
- To document **ovulation**: measurement of mid-luteal progesterone level, urinary luteinizing hormone using home prediction kit, and basal body temperature charting.
- To determine etiology if **ovulatory dysfunction** suspected: measurement of FSH, prolactin, thyroid-stimulating hormone, 17α-hydroxyprogesterone (if hyperandrogenism suspected), testosterone (if hyperandrogenism suspected).
- To assess **ovarian reserve** (women older than 35 years): measurement of FSH and estradiol levels on day 3 of the menstrual cycle, clomiphene citrate (Clomid) challenge test, or transvaginal ultrasonography for antral follicle count.
- To assess **tubes**, **uterus**, and **pelvis**: transvaginal ultrasonography, hysterosalpingography if tubal dysfunction suspected or evaluation otherwise unrevealing, hysteroscopy if results of hysterosalpingography suggest intrauterine abnormality, laparoscopy if results of hysterosalpingography abnormal or evaluation otherwise unrevealing.

Management of Infertility

- **Treatment** ***depends*** on the **cause** of **infertility**, but may ***include*** **counselling**, **fertility treatments**, which *include* **in vitro fertilization (IVF)**.

A) Couples Counselling

- **Ideal Coital Frequency**;
  - Consisting of intercourse on multiple days during the "fertile window," which includes the five days preceding and the day of anticipated ovulation, should be reviewed with the couple.
- ***Using* Methods *for* Fertility Awareness**;
  - **Clear-plan Easy Fertility Monitor** (Clearblue®); Detects both LH and estrogen hormones for optimal timing of intercourse.
  - **Urinary LH Kit**; Detect the LH surge.
  - **Saliva Ferning Test**; uses a tiny microscope (FertilFocus®) to view a drop of saliva once a day, in ovulation day it appear like tree paper.
  - **Basal Thermometer** (DuoFertility®); detect BBT.
  - ***Checking for* E-type Vaginal Mucus Discharge**; Clear and stringy in ovulation days.



Non-fertile
Only dots and some lines appear

Transitional
Some fern patterns start to appear

Fertile
A lot of ferning patterns appear

- ***Avoiding* lubricants** and **douches *should be* stressed**.
- ***Avoid* alcohol *consumption*** and ***use*** of **tobacco** and **street drugs** and ***limit* caffeine *intake***.
- ***Avoid any* drugs** that *may* **affect sperm count** or **reduce sexual function**.
- ***Avoid* stress** *may contribute* to ***reduced* sperm quality**.
- ***Treatment*** of **underweight women** (Body Mass Index; BMI = < 19 kg/m^2):
  - Underweight women are frequently hypoestrogenic and anovulatory.
- ***Treatment*** of **overweight women** (BMI = > 25 kg/m^2):
  - Overweight women are often anovulatory particularly with polycystic ovary syndrome (PCOS).

B) Assisted Reproductive Technology (ART)

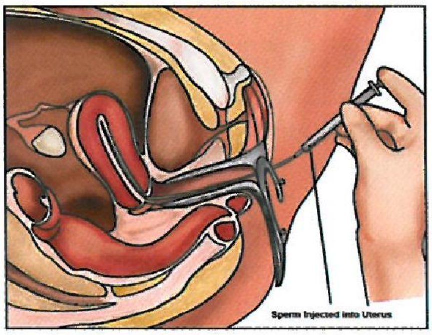
- **Assisted reproductive technology** (**ART**) is the **technology** *used to **achieve*** **pregnancy** in **procedures** such as **fertility medication**, **in vitro fertilization** and **surrogacy**.

Fertility Medications

- **Drugs** used for ***both*** **women** and **men** *include*;
  - A) **Selective Estrogen Receptor Modulators** (**SERMs**); **Clomiphene Citrate** (Clomid®) is used to induce ovulation in infertility in women and it is sometimes used in the treatment of male hypogonadism.
  - B) **Gonadotropin Preparations**
    - **FSH Preparations**; **Urofollitropin** (Fostimon®), **Follitropin Alfa** (Gonal-f®) and **Follitropin Beta** (Puregon®) are used in ovulation induction, spermatogenesis induction and in assisted reproductive technology (ART).
    - **LH Preparations**; **Lutropin Alfa** (Luveris®) is used for follicle stimulation only in combination with Follitropin.
    - **Human Menopausal Gonadotropin** (**hMG**) or **Menotropin** (Pergonal®) is used in assisted reproductive technology (ART).
    - **Human Chorionic Gonadotropin** (**hCG**) (Pregnyl®) Induction of ovulation, hypogonadism and in assisted reproductive technology (ART).
  - C) **Gonadotropin-releasing Hormone** (**GnRH**) **Analogues**; such as **Triptorelin** (Decapeptyl®) is used in assisted reproductive technology (ART) such as in vitro fertilization (IVF).
  - D) **Aromatase Inhibitors**; such as **Letrozole** (Femara®) is used for ovarian stimulation (has fewer side-effects than clomiphene and less chance of multiple gestation).
  - E) **Prolactin Inhibitors**; **Cabergoline** (Dostinex®) is used for hyperprolactinemic infertile women.
  - F) **Insulin Sensitizer**; **Metformin** (Glucophage®) is used for polycystic ovary syndrome (PCOS).
  - G) **Vitamins** and **Supplements**; many of vitamins and supplements can improve quality of sperm.

Intrauterine Insemination (IUI)

- IUI is a fertility treatment that uses a catheter to place a number of washed sperm directly into the uterus.
- The goal of IUI is to increase the number of sperm that reach the fallopian tubes and subsequently increase the chance of fertilization.
- Depending on the reasons for infertility.
- IUI may be selected fertility treatment with any of the following conditions:
  - Unexplained infertility or ejaculation dysfunction
  - Decrease sperm count and sperm mobility.
  - A hostile cervical condition, such as cervical mucus that is too thick.
  - Cervical scar tissue from past procedures or endometriosis.



In Vitro Fertilization (IVF)

- In vitro fertilization (IVF) is a process by which an egg is fertilized by sperm outside the body.
- There are 5 basic steps to IVF:
  - Step 1: Stimulation (called super ovulation).
  - Step 2: Egg retrieval (called follicular aspiration).
  - Step 3: Insemination and Fertilization.
  - Step 4: Embryo culture.
  - Step 5: Embryo transfer.

Intracytoplasmic Sperm Injection (ICSI)

- In ICSI, a single healthy sperm is injected directly into a mature egg.
- ICSI is often used when semen quality is a problem, there are few sperm, or if fertilization during IVF cycles failed.

Donor Eggs or Sperm

- Some couples may only be able to achieve pregnancy by using eggs or sperm from another person (the donor).

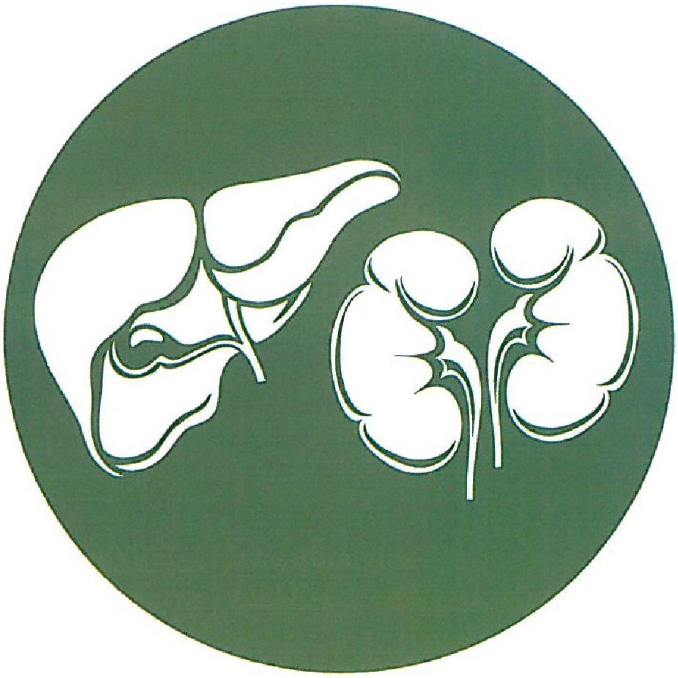
Surrogacy (Gestational Carrier)

- Women who don't have a functional uterus or for whom pregnancy poses a serious health risk might choose a gestational carrier.
- In this case, the couple's embryo is placed in the uterus of the carrier for pregnancy.

Liver & Kidney

(HEPATOLOGY & NEPHROLOGY)

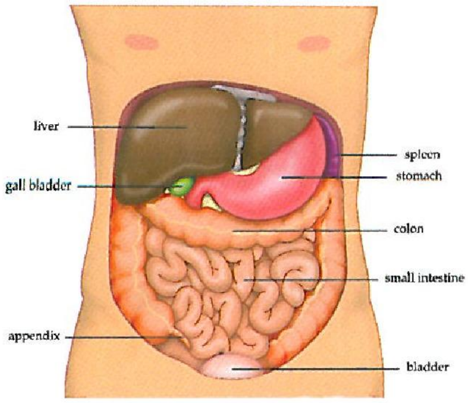
Subject	No. of page
Liver	
Introduction	**992**
Acute Liver Failure (ALF)	**997**
Liver Cirrhosis	**1003**
Kidney	
Introduction	**1009**
Acute Kidney Injury (AKI)	**1020**
Chronic Kidney Disease (CKD)	**1026**



Liver Diseases

Introduction

- **Liver** is the *largest* **gland** in the **body**.
- It is a ***very* vascular organ** (high blood flow), **soft**, **pinkish-brown, triangular organ**.
- A ***human*** **liver** ***normally*** **weighs 1.5 kg**.
- It is ***located*** in the **right upper quadrant** of the **abdominal cavity**, resting *just below* the **diaphragm**.
- The **liver** has **two large sections**, called the **right** and the **left lobes**.
- It ***detoxifies*** *various* **metabolites**, ***synthesizes*** **proteins**, and ***produces*** **biochemicals** *necessary for* **digestion**.
- The **gallbladder sits *under*** the **liver**, along with **parts** of the **pancreas** and **intestines**, ***stores*** **bile** *produced by* the **liver**.



Liver Functions

- **Carbohydrate Metabolism**;
  - **Glycogen *synthesis*** and **store**.
  - **Glycogenolysis** and **Gluconeogenesis**.
- **Lipid Metabolism**;
  - ***Synthesis*** of **Phospholipids**, **Cholesterol**, **Endogenous Triglycerides** and **Lipoproteins** (HDL & VLDL).
  - ***Degradation*** of **lipoproteins *remnant***.
  - ***Site*** of **β-oxidation** of **free fatty acid**.
- **Protein Metabolism**;
  - ***Deamination*** of **amino acid** and ***synthesis*** of **urea**.
  - ***Synthesis*** of *many* **plasma proteins** (**Albumin**) and ***most*** of **coagulation factors**.
- **Detoxification**:
  - ***Detoxify***, by ***metabolizing*** and/or ***secreting***, **drugs**, **alcohol** & ***other*** **toxins**.
- **Storage Function**:
  - ***Storage*** of **Glycogen**, **Vitamin D**, **Vitamin A**, **Vitamin B12** and **Iron**.
- **Excretory Function**:
  - ***Excrete*** **bilirubin** and **cholesterol**.
  - ***Produces*** and ***excretes*** **bile** (a yellowish liquid) *required for* ***emulsifying*** **fats** and ***help*** the ***absorption*** of **fat-soluble vitamin** (vitamins **A**, **D**, **E** & **K**).

Bile

- **Bile** is a ***complex*** of **fluid** *containing* **water**, **electrolytes** and ***organic molecules*** *including* **bile acids**, **cholesterol**, **phospholipids** and **bilirubin**.
- **Bile Function**; - **Bile acids**, ***help for*** **digestion** and **absorption** of **fats** and **fat-soluble vitamins** in the **small intestine** (*by acting as a surfactant that emulsifies them into micelles*).
  - *Many* **waste products**, *including* **bilirubin**, are *eliminated from* the **body** by ***secretion*** into **bile** and *elimination in* **feces**.
- **Gall bladder *stores*** and ***concentrates*** **bile** and **cholesterol** is ***soluble*** in **bile**.
- **Gallstone** (**Cholelithiasis**); is a ***stone formed within*** **gallbladder**, *about* **80%** of **patients** are ***asymptomatic***, ***most of which*** are **composed** *predominantly of* **cholesterol** (***develop*** when **bile** *contains* ***too much*** **cholesterol** and ***not enough*** **bile salts**).
- **Gallstone *Common Symptoms***; **biliary colic** (**crampy pain**; ***right* upper abdominal pain**, *usually* ***after*** **heavy meals** and ***lasts*** **1-4 hours**), ***more than*** **5 hours** → **Complication** (**biliary colic** ***more than*** **5 hours**, **fever**, ***persistent*** **tachycardia**, **hypotension** and **jaundice**).